Identification of dead regions within the cochlea using threshold equalising noise test (TEN) in patients who had chemotherapy with platinum based drugs.

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Identification of dead regions within the Cochlea using Threshold Equalising noise test (TEN) in patients who had chemotherapy with platinum based drugs

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SUMMARY (ABSTRACT)

Candidate's Surname: Berry

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Candidate for the Degree of MPhil

Title of Thesis: Identification of dead regions within the Cochlea using Threshold Equalizing noise test (TEN) in patients who had chemotherapy with platinum based drugs.

SUMMARY

(A) OBJECTIVE

To assess if platinum based chemotherapy causes dead regions in Cochlea

(B) METHODS

STUDY DESIGN

Prospective & longitudinal

YEAR OF STUDY

2005 -2009 (Part time as part of MPhil, University of Swansea)

DISEASE/ CONDITION STUDIED

Patients having chemotherapy with platinum chemotherapeutic drugs (Cisplatin, Carboplatin & Oxaliplatin) would be included and their hearing assessed by threshold equalising noise (HL) test for the presence of dead regions before initiation of therapy and then at 1, 6 & 12 months post treatment.

SUBJECTS STUDIED

50 patients were included.

Inclusions:

- Age 20-75 years, both male and female patients
- On chemotherapeutic agents
  - cisplatin (n=19)
  - carboplatin (n= 20)
  - oxaliplatin (n=11)

Exclusions:

- Middle or outer ear disease causing conductive hearing loss
- On other ototoxic drugs (past or present)
- Congenital hearing loss
- Patients who do not, or are unable to, consent to the trial
- Terminally ill patients

SETTING IN WHICH SUBJECTS STUDIED

TEN test was performed in a sound proof room within the Audiology department at Singleton hospital, Swansea.

INTERVENTION

Threshold Equalising noise test

OUTCOME MEASUREMENT

Identification of Dead region

(C) RESULTS

A total of seven subjects demonstrated dead regions, of which three had received Oxaliplatin, two received Cisplatin and two received Carboplatin. Another five subjects showed evidence of dead region at pre- chemotherapy stage, none of them had any previous history of chemotherapy with platinum based drugs, loud noise exposure, radiotherapy or use of ototoxic drugs. On reviewing the literature (search strategy: Oxaliplatin AND / OR hearing loss: 1966 to date), there has been only one report of a case of Oxaliplatin induced hearing loss.

(D) CONCLUSION

This study highlighted that administration of platinum based drugs leads to dead regions albeit at variable times. Dead regions can improve spontaneously and were also associated with use of Oxaliplatin.

Key words: TEN test; dead regions; platinum drugs

DECLARATIONS & STATEMENTS

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted for any degree.

Signed (Mr. Sandeep Berry)
Date 2/2/11

STATEMENT 1

This thesis is the result of my own investigations, except where otherwise stated. Where correction services have been used, the extent and nature of the correction is clearly marked in a footnote (s)

Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

Signed (Mr. Sandeep Berry)
Date 2/2/11
2/2/11

STATEMENT 2

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

Signed (Mr. Sandeep Berry)
Date 2/2/11

CONTENTS

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to Simon Browning for his patience, support, and help with the diagrams and guidance throughout the course of this degree and also to Prof. Gareth Jenkins, for his valuable direction and support.

I would like to express my genuine appreciation to all the patients who so kindly agreed to take part in the present study and this study would not have been possible without their involvement.

I would also like to convey my sincere gratitude to the staff within the Audiology department, Singleton hospital, for their support. In particular I would like to thank Rhys Meredith, Eira and Andrea for their help and constant encouragement.

Finally, my sincere thanks to my wife for her constant encouragement without which, I really would not have been able to complete this degree!

ILLUSTRATIONS

TABLES

ABBREVIATIONS

BM = Basilar Membrane

CF = Characteristic Frequency

DR = Cochlear Dead Region

dB = Decibel

ERB = Equivalent Rectangular Bandwidth

ERB_N = Equivalent Rectangular Bandwidth of an auditory filter as determined using young, normally hearing subjects tested at moderate sound levels

f_e= Dead Region Edge-Frequency

HL = Hearing Level

IHC = Inner Hair Cell

OHC = Outer Hair Cell

PTA = Pure Tone Audiometry

PTC = Psychophysical Tuning Curve

SNHL = Sensorineural Hearing Loss

SPL = Sound Pressure Level

TEN = Threshold equalizing noise

CHAPTER 1
INTRODUCTION

1.1 Rationale

1.2 Anatomy

1.3 Physiology

1.4 Platinum based chemotherapy drugs

1.5 Dead Regions

1.6 Threshold Equalising noise test (TEN)

1.7 Methodology

1.8 Aim

1.1 Rationale

Cochlear hearing loss can arise from different causes and is often associated with damage to hair cells within the cochlea. Inner hair cells (IHC) at certain places along the basilar membrane may be non-functional or even missing thereby leading to no transduction of basilar membrane vibration at those places. In addition to the above, the auditory neurons associated with certain places may be non-functioning or degenerated. This means that the information about basilar membrane vibration at those places is not transmitted to the brain.

The pattern of damage to IHC is never mentioned in the literature in human models because it was not possible to detect this by using simple pure tone audiometry (Freilich *et al.*, 1996). Established tests for detection of outer hair cell (OHC) function are pure tone audiometry and Otoacoustic emissions (Stavoulaki *et a.l*, 2001). The complete loss of IHC over certain region of basilar membrane is called a dead region. Dead regions do not occur in people with normal hearing, except perhaps at very high frequencies above the normal audiometric range (Moore,2005-personal communication).

1.2 Anatomy

The ear, which houses the peripheral parts of the auditory and vestibular apparatus, is descriptively divided into the external, middle and internal ear. The external ear consists of the auricle or pinna and the external acoustic meatus at the medial end of which lies the tympanic membrane, separating the external ear from the middle ear. The middle ear or tympanic cavity (tympanum) is a small space in the temporal bone containing the auditory ossicles (malleus, incus & stapes) and air that communicates with the nasopharynx by the Eustachian tube. By its medial wall, the middle ear adjoins the inner ear, which is composed of the osseous labyrinth, another space within the temporal bone, inside which is the membranous labyrinth containing the auditory and vestibular nerve receptors.

1.3 Physiology

The peripheral auditory system is a complex arrangement of various structures allowing conduction of acoustic vibrations from the external ear to the inner ear fluids and subsequent transduction of sound into electrical messages. Sound is essentially vibrations in air of air molecules and has two basic properties namely:- Loudness (subjective correlate of intensity) & Pitch (subjective correlate of frequency).

1.4 Dead Regions

Cochlear hearing loss can arise from different causes and it is often associated with damage to hair cells within the cochlea. Inner hair cells at certain places along the basilar membrane may be non-functional or even missing, thereby leading to no transduction of basilar membrane vibration at those places. In addition to the above, the auditory neurons associated with certain places may be non-functioning or degenerated. This means that the information about basilar membrane vibration at those places is not transmitted to the brain. Areas where there are no functioning IHC are referred to as dead regions.

1.5 Platinum based chemotherapy drugs

Platinum chemotherapeutic drugs like cisplatin, carboplatin and oxaloplatin have an established place in the management of certain malignancies. Their use, however, is associated with hearing loss amongst other things (e.g. hair loss, nausea, sub-fertility). Ototoxicity is one of the main side effects of cisplatin treatment. Initial signs of cisplatin ototoxicity usually become known 3-4 days after drug administration and tend to affect the higher frequencies. Even though not life threatening, ototoxicity of cisplatin is considered to be a serious side effect and therefore dose limiting (Laurell et al, 1987). Several factors have been implicated for higher toxicity; these include prior or concomitant radiation, pre-existing hearing loss, decreased renal function, concomitant use of other ototoxic drugs, faster infusion rates, very young age, older age, larger dose and higher cumulative dose. Carboplatin is less ototoxic than cisplatin and its anti-neoplastic activity is equivalent to that of cisplatin. However, optimal use of carboplatin is limited by its ototoxic effects (Hussain et al., 2004).

Macdonald et al, showed in an animal model that there is damage to IHC in the basal turn of cochlea, leading to higher frequency hearing loss following use of carboplatins, the mechanism for which is unknown (Macdonald et al., 1994). Oxaliplatin is a new anticancer chemotherapeutic agent belonging to the platinum complex series. On extensively reviewing the literature, there has been only been one report of a case of Oxaliplatin induced hearing loss.

1.6 Threshold Equalising Noise (TEN) test

Several researchers have looked into ways of using masking noise to ascertain the presence of dead regions (Halpin *et al.*, 1994 & Humes *et al.*, 1984). Pyschophysical tuning curves (PTC) are often considered the gold standard for the detection of dead regions. However, there are certain factors that can complicate the interpretation of the PTC. PTC's are a valuable useful research tool but are time consuming. Hence the search for a simpler test led to development of the threshold equalising noise (TEN) test.

Moore (2000) first described a simple way of detecting these dead regions by using a hearing test called the Threshold equalizing noise (TEN) test. This involves detection of tones in the presence of ipsilateral TEN using the principles of noise audiometry. This is a short and simple test available on a CD. A dead region is present when the masked threshold is at least 10 dB higher than the absolute threshold and at least 10 dB above the level of masking noise (Moore *et al.*, 2000)

1.7 Methodology

A prospective longitudinal study was conducted to identify the presence of dead regions in the cochlea of patients who have had chemotherapy with platinum based drugs using TEN (HL) test. Fifty patients having chemotherapy with platinum chemotherapeutic drugs (Cisplatin, Carboplatin & Oxaliplatin) were recruited and their hearing assessed by Pure Tone Audiometry and the TEN (HL) test for the presence of dead regions before initiation of therapy and then at 1, 6 & 12 months post treatment, as it is unknown in the literature about the occurrence of the dead regions with regards to the administration of platinum based drugs.

Inclusions:

- Age 20-75 years, both male and female patients
- On chemotherapeutic agents (cisplatin, carboplatin and oxaliplatin)

Exclusions:

- Middle or outer ear disease causing conductive hearing loss
- On other ototoxic drugs (past or present)
- Congenital hearing loss
- Patients who do not, or are unable to, consent to the trial
- Terminally ill patients

1.9 Aim

The primary aim of this thesis is therefore:

To identify dead regions within the cochlea using Threshold Equalising noise (TEN HL) test in patients who had chemotherapy with platinum based drugs.

CHAPTER 2

ANATOMY OF THE EAR

2.1 Introduction

2.2 Components of ear

(i) External ear
(ii) Middle ear
(iii) Inner ear

2.3 External ear

(i) External auditory canal
(ii) Pinna (auricle)
(iii) Tympanic membrane

2.4 Middle ear cleft
2.5 Inner ear

(i) Cochlea

2.6 Conclusion

2.1 Introduction

This chapter provides a brief description of the most basic features of the anatomy of the ear. The ear, which houses the peripheral parts of the auditory and vestibular apparatus, is descriptively divided into the external, middle and internal ear. The external ear consists of the auricle or pinna and the external acoustic meatus, at the medial end of which lies the tympanic membrane, separating the external ear from the middle ear. The middle ear or tympanic cavity (tympanum) is a small space in the temporal bone containing the auditory ossicles (*Malleus, incus & stapes*) and air that communicates with the nasopharynx by the Eustachian tube. By its medial wall, the middle ear adjoins the inner ear, which is composed of the osseous labyrinth, another space within the temporal bone, inside which is the membranous labyrinth containing the auditory and vestibular nerve receptors.

2.2 Components of Ear

The ear is broadly divided into

(i) External ear

(ii) Middle ear cleft

(iii) Inner ear

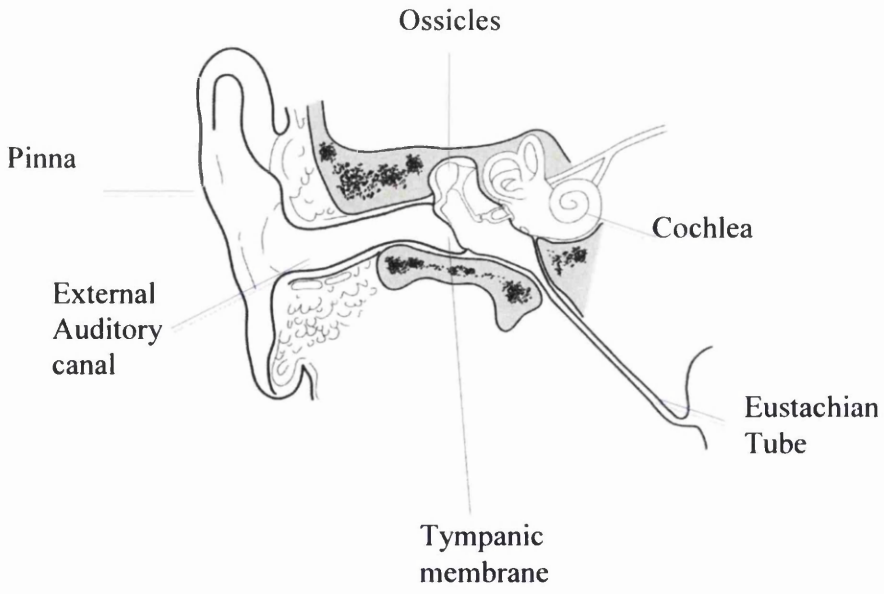


Figure 2.2 Components of the Ear

2.3 External Ear

The external ear is composed of:

1. External ear canal
2. Pinna (auricle)
3. Tympanic membrane

(i) External Auditory canal

The external ear canal in adults is 2.5cm long with lateral one- third having cartilaginous walls and the medial two- thirds bony walls. The continuing curve of the deep bony canal results in the tympanic membrane lying at a slant across the bony canal with an acute angle between the drum and anterior canal wall.

(ii) Pinna (auricle)

The body of the auricle is made up of elastic fibrocartilage and is a continuous sheet except for a narrow gap between the tragus and anterior crus of helix, where it is replaced by dense fibrous tissue band. Both pinna and external auditory canal, from anatomical aspect, provide protections of the tympanic membrane (and the middle ear beyond) from direct injury, act as a directional amplifier of sound and provide important cues for sound localization. Pinna and external ear canal are now recognized as significant components and are far from being vestigial in function.

(iii) Tympanic membrane

The tympanic membrane is slightly oval in shape and is approximately 9-10 mm in its maximum diameter from postero superior to anterosuperior. It is like a curved cone with a single layer of squamous epithelium on canal side and a single mucosal layer on the middle ear side with an intervening layer composed of fibrous tissue. This layer is composed of collagen fibres aligned in a radial and circular fashion. Tympanic membrane vibrates in response to sound energy and transmits the resulting mechanical vibrations to the structures of the middle ear.

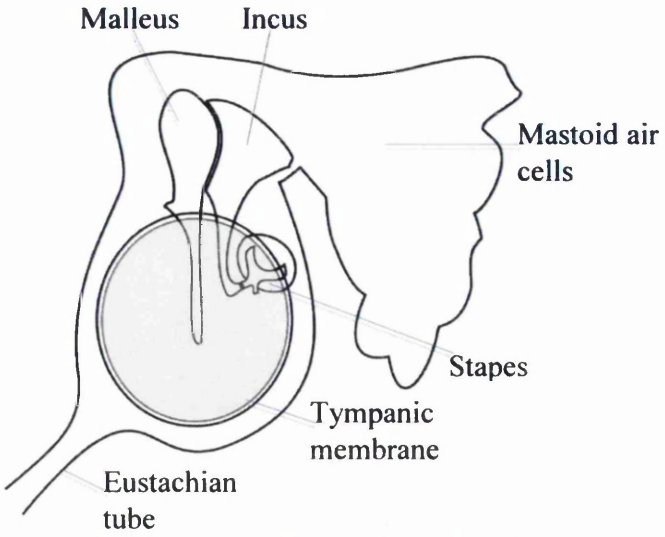


Figure 2.4 Middle ear Cleft

2.4 Anatomy of middle ear cleft

The middle ear cleft consists of a centrally filled space - the tympanum, its connection to the pharynx (Eustachian tube) and its extension to the neighbouring region of temporal bone.

The different parts of the middle ear cavity are: -

1. Eustachian tube
2. Tympanic (middle ear) cavity
3. Aditus ad antrum
4. Mastoid antrum
5. Mastoid air cells
6. Ossicles (*malleus, incus & stapes*)

The ossicles (*malleus, incus & stapes*) form a semi – rigid bony chain for conducting sound and their primary function is to amplify sound and act as an impedance-matching device, to compensate for the difference in impedance between air and the fluids of the inner ear.

7. Two muscles namely Tensor tympani and Stapedius

Both the tensor tympani and the stapedius are the smallest striated muscles in the body and are enclosed within the middle ear cavity. The tensor tympani muscle attaches to the medial aspect on the upper part of the handle of malleus and the

stapedius muscle emerges from the pyramidal eminence to attach to the upper part of the posterior crus of the stapes. They play an active role in the acoustic reflex, in addition to supporting and stiffening the ossicular chain. Contraction of both muscles is primarily activated by acoustic stimulation of 70-90 dB above threshold and thus, they protect the inner ear from excessive and potentially damaging loud noise exposure.

2.5 Inner ear

The inner ear lies within the petrous part of the temporal and consists of bony labyrinth enclosing a membraneous labyrinth. Perilymph lines the space between bony and membraneous labyrinth while endolymph fills the membraneous labyrinth and contains sensory cells of hearing and balance.

The inner ear is divided into the cochlea, which is responsible for transduction of sound into neural activity and the vestibular apparatus, which is responsible for assisting in balance.

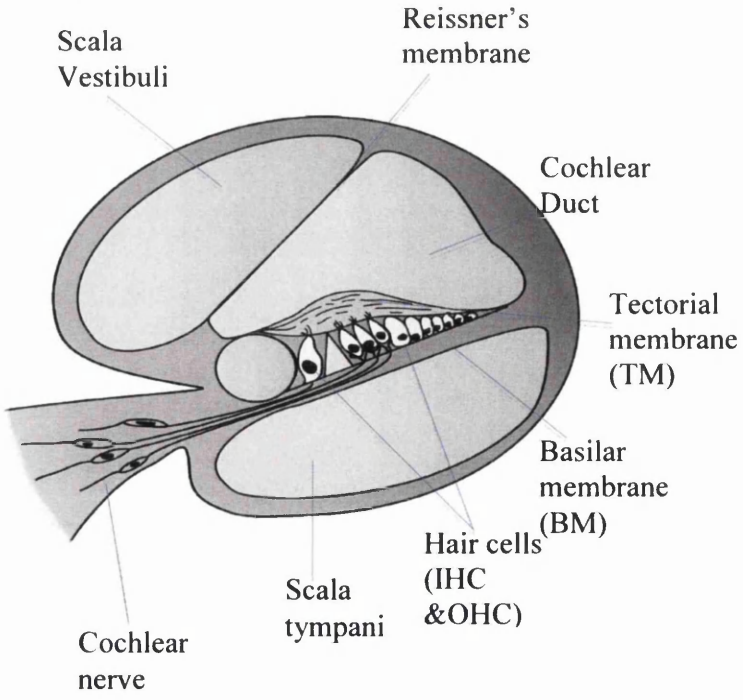


Figure 2.5 Inner Ear

(i) Cochlea

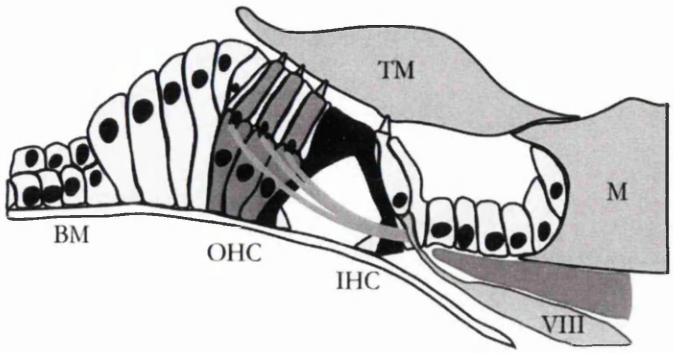
The bony cochlea has a coiled shell like appearance and houses a spiral structure, a part bone, a part membrane called the cochlear duct or scala media. This contains endolymph and sensory cells of hearing.

(a) Cochlear duct

It is triangular in section and spirals approximately two and half turns from base to apex. The human cochlear duct has a length of approximately 35mm. The duct has a flat floor called the spiral lamina, a sidewall that is mainly stria vascularis and a sloping diagonal roof called Reissner's membrane. Stria vascularis is the upper end of spiral ligament (thickened outer periosteum of the cochlear duct) comprised of numerous capillaries and blood vessels and involved in production of endolymph. The spiral lamina of the cochlea runs around a central bony core called the modiolus. At the apex of the modiolus the spiral lamina tapers off into the fluid filled spaces of the apex of cochlea. The spiral lamina has a bony portion – the bony spiral lamina attached to the modiolus - and a membranous portion or basilar membrane, which extends from the edge of bony spiral lamina to the outer wall of the labyrinth.

(b) Organ of Corti

This is a band like structure situated on the basilar membrane and contains auditory hair cells. These sensory cells have hair like stereocilia projecting from their upper, endolymphatic surfaces and are called hair cells. There are two types of auditory hair cells, the inner hair cells (IHC) and outer hair cells (OHC). The IHC lies closer to the modiolus than the OHC and has a rounded flask like shape. It is surrounded by supporting cells and has about 10 separate afferent auditory nerve fibres that make synaptic connection with its basal end. There are approximately 3,500 IHCs and 12,000 OHCs in healthy human cochlea. Between the IHCs and OHCs is a triangular space called the tunnel of Corti. The roof of this formed by the arch of processes of the inner and outer hair pillar cells. Each OHC is cylindrical in shape and is supported at its lower pole by the cup like processes of Deiters' cells.



BM: Basilar membrane
OHC: Outer hair cells
IHC: Inner hair cells
VIII: Cochlear nerve
TM: Tectorial membrane
M: Modiolus

Figure 2.5 (i) b Organ of Corti

The body of OHC is therefore surrounded by a space that is filled with a fluid called cortilymph, which has probably the same composition as perilymph. The OHC only contribute a little to the afferent innervation arising from cochlea but they have a good efferent supply coming from various tunnel crossing fibres that in turn derive from the olivocochlear bundle. There are approximately 12,000 OHCs in each organ of corti. The apical surfaces of the OHC and IHC have stereocilia projecting from them into the endolymph. Each of the stereocilia in a bundle on one hair cell is linked by very fine links to the adjacent stereocilia (see section 3.6). The tips of shorter stereocilia also have links to the adjacent taller stereocilia and it is these links that are thought to be responsible for the opening of ionic channels during auditory stimulation.
The tectorial membrane arises from a lip or limbus on the edge of bony spiral lamina. The membrane, which is a fibrogelatinous structure, spreads outwards across the organ of corti and in life, attaches to the supporting cells, which lie on the outer side of the OHCs. The tips of the longest stereocilia of the OHC insert a little way into the tectorial membrane (Wright, 1997).

2.5 Conclusion

The basic knowledge of the relevant clinical anatomy of the ear is essential in the context of this thesis, as it helps in understanding the effects of platinum based chemotherapeutic drugs on the inner ear.

CHAPTER 3

PHYSIOLOGY OF THE EAR

3.1 Introduction

3.2 Physiology of sound conduction

3.3 Tonotopic distribution & basilar membrane

3.4 Role of Outer hair cells

3.5 Role of Inner hair cells

3.6 Molecular physiology

3.7 Conclusion

3.1 Introduction

The peripheral auditory system is a complex arrangement of various structures allowing acoustic energy, in the form of sound waves, to be channeled into the ear canal by the pinna. Sound waves strike the tympanic membrane, causing it to vibrate like a drum, and changing it into mechanical energy. The malleus, which is attached to the tympanic membrane, starts the ossicles into motion. (The middle ear components mechanically amplify sound). The stapes moves in and out of the oval window of the cochlea creating a fluid motion. The fluid movement within the cochlea causes membranes in the Organ of Corti to shear against the hair cells. This creates an electrical signal, which is sent via the Auditory Nerve to the brain, where sound is interpreted.
This chapter explains this process in more detail.

3.2 Physiology of sound transduction

Sound is essentially vibrations in air of air molecules and a sound wave has two basic properties namely: -

1. Loudness – subjective correlate of intensity
2. Pitch – subjective correlate of frequency

The purpose of the Cochlea is to transduce vibrations into neural activity. These vibrations displace the cochlear fluids, producing a wave of displacement that travels along the Basilar membrane, which reaches, from the base to the apex of the cochlea, which increases in amplitude before decreasing fairly abruptly (Pickles, 2005; Moore, 2007). Response to a sound of a given frequency is determined by the mechanical properties of the basement membrane, being narrow and stiff at the basal end and responding preferentially to high-frequency sounds. Conversely, low-frequency sounds are better appreciated at the apex, where it is wider and more flexible (Pickles, 2005).

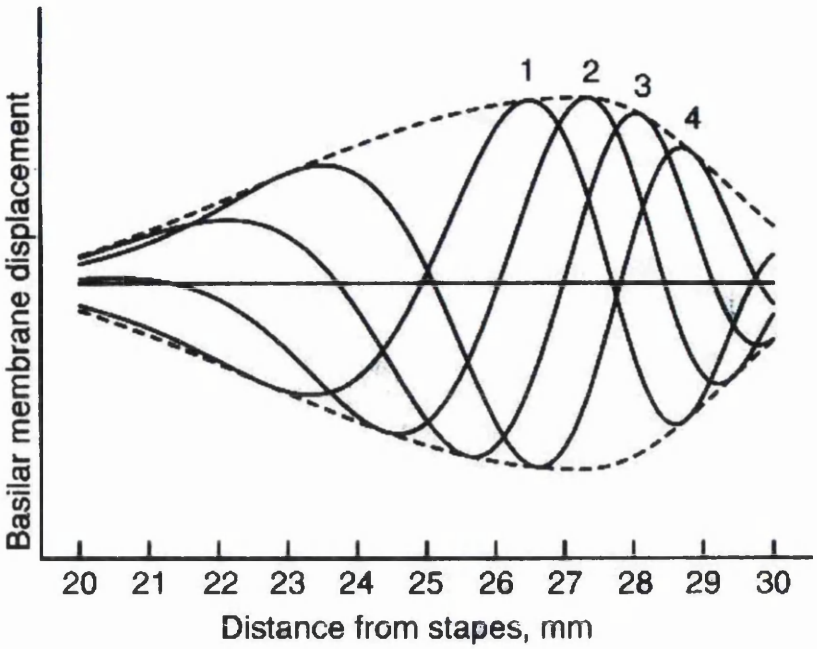


Figure 3.2 Illustration of travelling wave (BM displacement/distance from stapes). The solid lines illustrate the instantaneous displacement of the BM at four successive instants in time (labelled 1-4). The pattern moves from left to right, increasing gradually with distance and reducing rapidly after the point of peak displacement (Moore, 2007, p .12)

3.3 Tonotopic distribution & basilar membrane

The basilar membrane (BM) is tonotopically structured with each point along its length responding with maximum resonance to a certain sound frequency termed the characteristic frequency (CF) (Pickles, 2005). The deformation of the basilar membrane is a traveling wave. When motion of the stapes establishes a sound wave in the fluid of the inner ear, each small region of the basilar membrane deflects in response to this pressure with a time delay that depends upon its own mechanical properties. The wave then diminishes rapidly in both amplitude and velocity as it continues to move toward the apex. The area of basilar membrane nearest to the oval window resonates best to sounds of high frequency whereas low frequency sounds resonate the apex better. This is due to the mechanical properties of the basilar membrane as it is narrow and stiffer at the base than it is at apex, thereby leading to

decrease in its resonance frequency as sound waves travel away from oval window towards the apex.

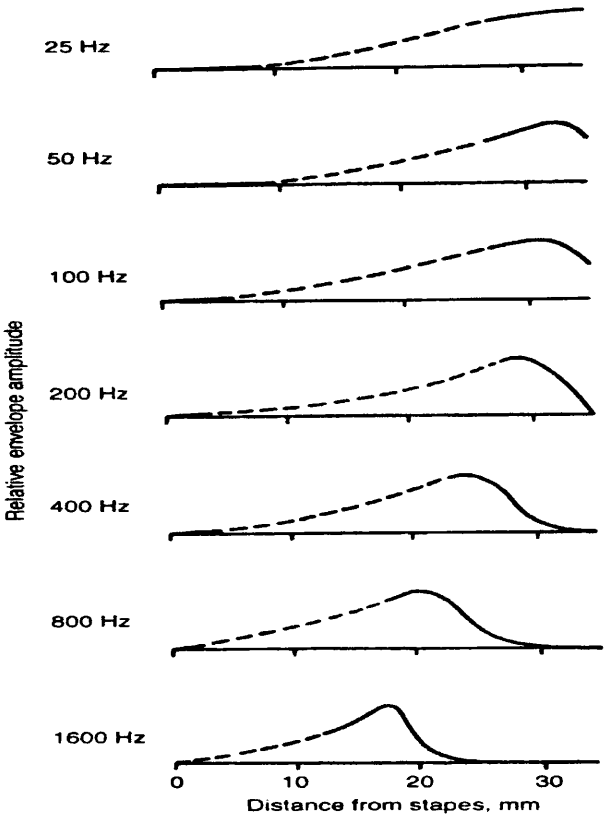


Figure 3.3 Demonstration of the envelope of patterns of vibration along the BM for low-frequency sounds (Moore, 2007, p. 14)

3.4 The Role of Outer Hair cells (OHC)

Outer hair cells reside within the Organ of Corti (figure 2.5 b) supported by Deiters' cells and Hensen's cells and are susceptible to damage by ototoxic drugs, noise exposure, metabolic changes and infection. The stereocillia of OHC's are in contact with the tectorial membrane, which lies above them throughout the length of the cochlea. The depolarization of OHCs, (see section 3.6) resulting from movement of their respective stereocilia, results in their expansion and contraction, influencing the response of the BM to sound (Pickles, 2005).

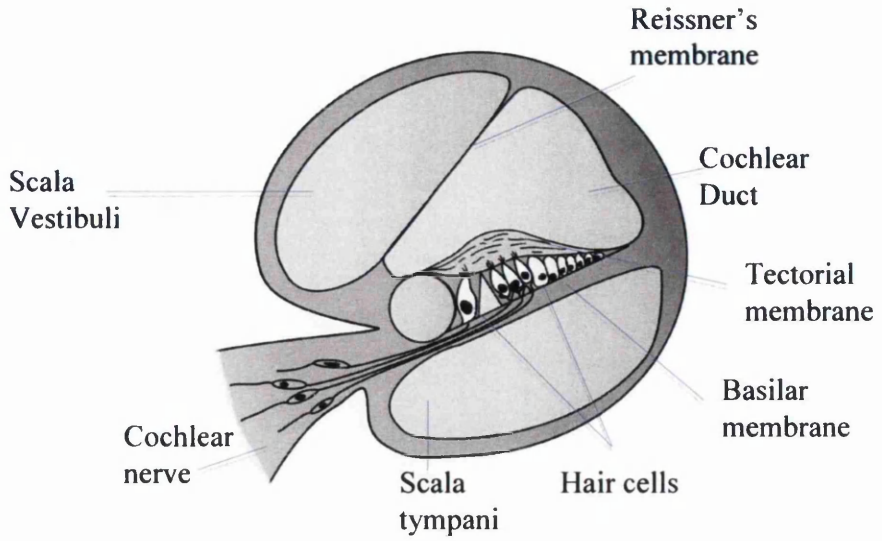


Figure 3.4 Components of the Inner ear

The OHC's play a role in the active mechanism of the cochlea by changing their own stiffness and length in response to the vibrations of the sound wave. This activity of the outer hair cells enhances the responses to weak sounds (increasing the amplitude of vibration) and sharpens the tuning on the basilar membrane, thereby increasing the frequency selectivity of the auditory system i.e. its ability to separate out the different frequencies that are present in complex sounds such as speech and music. The amplified vibrations are then detected by the inner hair cells (IHC), which form a single row running along the length of the basilar membrane. In response to the vibrations on the basilar membrane, IHC's generate electrical signals and release neurotransmitter and this in turn leads to neural activity in the auditory nerve.

3.5 The Role of Inner Hair Cells

There are 3,500 Inner hair cells (IHCs) in a healthy human cochlea and they have a large synaptic contact with the afferent nerve fibres of the auditory nerve. They are the true sensory receptors in the cochlea and their primary role is to convey sound information through a process of transduction in response to basilar membrane vibrations.

Cochlear hearing loss is often associated with damage to the hair cells thereby leading raised hearing thresholds. OHC's injury causes impairment of the active mechanism

in the cochlea, which results in reduced basilar membrane. Hence the sound level must be larger than normal to give a just detectable amount of vibration. On the other hand, IHC damage can lead to a less efficient stimulation of the auditory nerve.

3.6 Molecular Physiology

Hair cells (inner & outer) have apical stereocilia made up of actin filament inserted into the cuticular plate, although the stereocilia of the IHC do not touch the tectorial membrane. These are aligned in four rows with the tallest one being at the most lateral side of the hair cell. Stereocilia are linked with each other at their tips which project into the endolymph (high concentration of potassium ions) while the body of the hair cells is bathed in Perilymph (high in sodium ions and low in potassium ions). A strong electrochemical gradient exists between the endolymph and intracellular space. Sound waves cause deflection of the stereocilia towards the tallest cillium, resulting in the opening of the ion channels at the tip links. This results in the inflow of potassium ions intracellularly causing depolarization of cell body, opening of voltage gated calcium channels and release of the neurotransmitters. IHC release Glutamate into synaptic spaces causing activation of afferent nerve fibres. OHC, on the other hand, following depolarization exhibit electromotility and thus contribute to shaping the mechanical excitation of the IHC (Pickles, 1997)

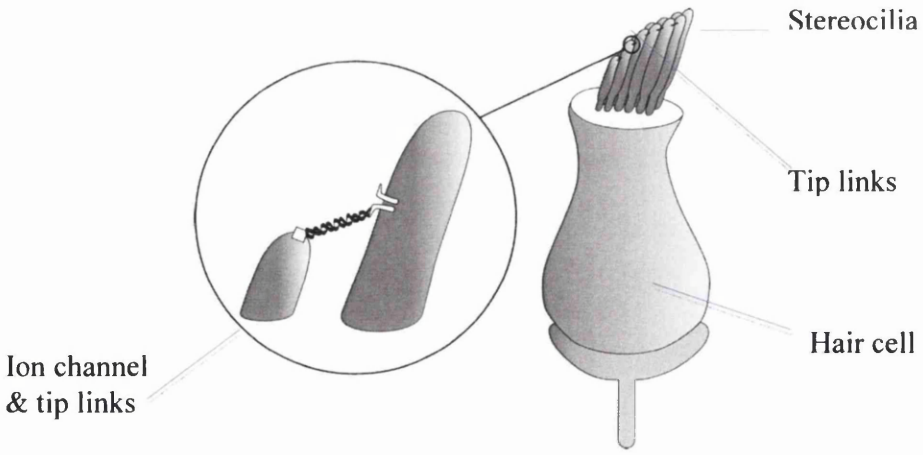


Figure 3.6 Molecular Physiology

Whilst OHCs are more susceptible to damage than IHCs it is possible, though rare, for there to be intact OHCs but damaged IHCs. Consequently sharp tuning contributed by OHCs is preserved. However, damage to IHCs results in increased absolute thresholds. Increased BM vibration is required to produce 'threshold' amounts of neural activity for their respective CFs. Complete loss of (or significantly damaged) IHCs results in distorted perception of sound frequencies corresponding to the CFs of those IHCs. Generally, with severe hearing loss, there is an absence of both OHCs and IHCs, resulting in a combination of the above effects (Moore, 2007)

3.8 Conclusion

This chapter provides a basic outline of the physiology of hearing process and will be helpful in the understanding of pathophysiological effects of the platinum based chemotherapeutic drugs on the inner ear in the following chapter.

CHAPTER 4

PLATINUM BASED CHEMOTHERAPY DRUGS

4.1 Introduction

4.2 Platinum based chemotherapy drugs

(i) Cisplatin
(ii) Carboplatin
(iii) Oxaliplatin

4.3 Preventing & monitoring Ototoxicity

4.4 Conclusion

4.1 Introduction

Medicines procured from herbs, soil or animals have been used for humans since the dawn of civilization. Drug induced hearing loss was first reported about 1000 years ago by Abu Ali al-Husayn ibn Abd-Allah ibn Sina, who is better known as Avicenna and the author of 'Canons on Medicine'. He stated in his book that the use of mercury vapours to kill head lice led to hearing loss (Schacht, 2006). The first well documented drugs associated with hearing loss were salicylate and penicillin (Stephens, 1982).

The modern era of chemotherapy came with the discovery and synthesis of Salvarsan, an arsenical drug for treatment of syphilis, by Paul Ehrlich. A number of cases of cochlear nerve deafness emerged following the introduction of Salvarsan and it has the dubious honour of being labelled as the first modern drug to be linked with undesirable effects on the ear (Schacht and Hawkins, 2006).

Cisplatin (cis-diamminedichloro-platinum) was first synthesized in 1845 but it was only after 125 years that its anti-neoplastic potential was discovered and first clinical trials published. However, with the celebrated efficacy of cisplatin against various tumours came many side effects with ototoxicity being one of them. The primary targets of cisplatin ototoxicity are the outer and inner cells and the stria vascularis. Carboplatin, its sister drug, seems to be less ototoxic but has a predilection for the inner hair cells. The reported incidence of cisplatin ototoxicity in the literature varies from 9% to 91% (Ryback *et al.*, 1981).

Ototoxicity is defined as the tendency of certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner ear and especially of the end organs and neurons of the cochlear and vestibular divisions of the VIII cranial nerve. Ototoxicity has been divided in five grades by the National Cancer Institute (Williams *et al.*, 1995). These are as follows: -

Grade 1: None or no change in hearing level

Grade 2 : Asymptomatic, hearing loss on audiometry only

Grade 3: Tinnitus & asymptomatic hearing loss

Grade 4: Hearing loss interfering with function, correctable with hearing aid

Grade 5: Deafness not correctable

4.2 Platinum Based chemotherapy drugs

Platinum-based natural metal derivatives were found to be useful for cancer treatments around 150 years ago with the synthesis of cisplatin. However, their clinical use did not commence until 30 years ago. Platinum-based chemotherapy agents work by cross-linking subunits of DNA. These agents act during any part of the cell cycle and help in treating cancer by impairing DNA synthesis, transcription, and function. The platinum based chemotherapeutic drugs include:

1. Cisplatin
2. Carboplatin
3. Oxaliplatin

4.2 (i) Cisplatin

(a) Introduction

Cis-platinum (Cis-diamminedichloro platinum II) is a metal co-ordination complex whose chemical structure is unique among current chemotherapeutic agents (Ryback *et al*, 1981). Two main side effects noted are tinnitus and hearing loss, which can occur simultaneously or separately. Hearing loss is often permanent, or may be partially reversible although complete recovery has been reported (Aguilar-Markulis *et al*, 1981).

(b) Pathophysiology

Morphological studies have been carried out to look at the damage caused by use of cisplatin on the inner ear of guinea pigs (Fleischman *et al.*, 1975) as well as rhesus monkeys and humans (Wright & Schaefer 1982). The biochemical mechanism of hearing loss caused by cisplatin is still a mystery (Blakely *et al.*, 1993). However, the most notable morphological alteration as a result of cisplatin administration is the destruction and degeneration of the outer hair cells of organ of corti as well as the inner hair cells. Komune (1981) and Boheim & Ekkehard (1985) reported atrophy of the stria vascularis and collapse of Reissner's membrane as result of cisplatin use. First, the outer hair cells near the base of the cochlea are affected and then the damage progresses apically and to inner hair cells. Initial signs of cisplatin ototoxicity usually become known 3-4 days after drug administration and tend to affect the higher

frequencies. Even though not life threatening, ototoxicity of cisplatin is considered to be a serious side effect and therefore dose limiting (Laurell *et al.*, 1987). Cisplatin induced hearing loss is usually bilateral and symmetrical but asymmetry can exist (Vermorken *et al.*, 1983).

There is a wide individual variability in the dose needed to produce an ototoxic effect. A simple dose to effect relationship does not seem to exist for cisplatin ototoxicity. The incidence of hearing loss is markedly high in those receiving single high dose injections, which may suggest a correlation between ototoxicity and peak plasma concentrations (Reddell *et al.*, 1982). Cisplatin binds extensively to albumin and other serum proteins and the active cytotoxic component of cisplatin is in the unbound portion.

(c) Review of Literature

Some reports in the literature have indicated that there may be risk factors associated with cisplatin ototoxicity. The reported incidence of cisplatin ototoxicity in literature varies from 9 to 91%. On reviewing the literature, there appears to be no clear consensus as to whether age or pre-existing hearing loss are risk factors for cisplatin induced hearing loss (Blakley *et al.*, 1994). A pre-existing hearing loss does not increase the ototoxic effects of cisplatin (Piel *et al.*, 1974). It has been suggested that hearing will not worsen even if chemotherapy is continued. This has been labelled as a plateau effect (Kopelman *et al.*, 1988). Laurel & Borg (1988) reported that neither age nor pre-existing hearing loss is a risk factor for cisplatin ototoxicity. Concurrent or adjuvant administration of cisplatin along with radiotherapy can potentiate hearing loss especially in the high frequencies (Low *et al.*, 2006). Ototoxicity by cisplatin can also occur in a cumulative manner after several low dose injections (Aguilar-Markulis *et al.*, 1981).

Blakley (1994) in their study looked at the risk factors for ototoxicity due to cisplatin. They assessed the hearing of a cohort of 42 patients with head and neck cancer undergoing chemotherapy with cisplatin. According to them, cisplatin binds to albumin and the active form remains in an unbound state. They hypothesized that protein-binding effects are responsible for greater toxicity when albumin levels are low. In addition, when the oxygen carrying capacity of the blood is low, the inner ear is more susceptible to damage. This may be directly due to chemical oxidation –

reduction reactions. However, the data from their study did not pinpoint any specific mechanism for cisplatin- induced ototoxicity. It seems reasonable to state that any measures that optimise tissue oxygenation may decrease the ototoxic effects of cisplatin.

Skinner (1990) reviewed 22 children who received cisplatin for solid tumours and assessed their hearing. They concluded that cisplatin usage led to high frequency hearing loss with significant hearing loss being noted in all patients but one. It seems that the severity of hearing loss in individual children tended to increase with higher cumulative dose of cisplatin with high frequency loss appearing to stabilise after 600mg/m^2 body surface area.

Rademaker-Lakhai (2006) looked at the auditory toxicity associated with dose- and schedule- intensive cisplatin/gemcitabine chemotherapy in non–small-cell lung carcinoma patients. A total of 328 audiograms were analysed with a majority of patients demonstrating, a decrease in hearing thresholds at dosages above 60 mg/m^2 body surface area of cisplatin at the higher frequencies. Pure tone audiometry at 1, 2, and 4 kHz showed a mean hearing loss of 19 dB after cisplatin administration at dosages above 90 mg/m^2 body surface area. Threshold shifts at 8 and 12.5 kHz after cisplatin administration were experienced at dosages above 60 mg/m^2 body surface area. They concluded that hearing loss after cisplatin therapy occurs mainly at high frequencies and at dosages higher than 60 mg/m^2 body surface area. It is more pronounced when cisplatin is given once every 2 weeks. Pigmentation of the iris may influence susceptibility of an individual to cisplatin ototoxicity and cause high frequency sensorineural hearing loss but the mechanism remains unclear (Todd *et al.*, 1995).

4.2 (ii) Carboplatin

(a) Introduction

Carboplatin [cis –diamine (1,1-cylcobutanedicarboxylate) platinum (II)] is used as an alternative drug in oncology for treating small cell lung cancer, ovarian cancer, and carcinomas of the head and neck among many other types of cancer. It was introduced in the late 1980s and has since gained popularity in clinical treatment due to its vastly reduced side effects compared to its parent compound cisplatin. The antitumour

action of carboplatin is mediated by alkylation of DNA, which causes the killing of the cancerous cells (Los *et al.*, 1993)

(b) Pathophysiology

Carboplatin is less ototoxic than cisplatin and its anti-neoplastic activity is equivalent to that of cisplatin. Carboplatin causes ototoxicity by a direct effect on inner hair cells at the base of the cochlea. Oxidative stress to inner hair cells and cochlea could be direct consequence of carboplatin-induced ototoxicity. Ototoxicity is dose dependent and cumulative and rarely due to neural damage and tinnitus usually is the first symptom (Hussain *et al.*, 2004).

(c) Review of Literature

Carboplatin ototoxicity has been well reported in the literature. Carboplatin may cause subclinical or overt ototoxicity in 15% and 1% of the patients, respectively (Canetta *et al.*, 1987). Rosell (1999) detected 3% of any grade and less than 1% of severe (grade 3) ototoxicity in 306 patients with non–small-cell lung cancer patients receiving carboplatin-paclitaxel combination in their study. Parsons (1998) observed ototoxicity in 82% of children treated for neuroblastoma where carboplatin was used as part of the treatment regimen.

Du Bois (2003) reported 0.3% grade 3 ototoxicity without any grade 4 ototoxicity, in patients with ovarian cancer treated with paclitaxel-carboplatin combination regimen.

4.2 (iii) Oxaliplatin

Oxaliplatin is a new anticancer chemotherapeutic agent belonging to the platinum complex series. Two platinum derivatives, cisplatin and carboplatin, were until recently the only platinum compounds used clinically. It exerts its anti-tumour effects by platinum-adduct formation, binding to cellular proteins and possibly interfering with RNA synthesis as well.

These products have major activity in a variety of solid tumors, such as testicular, ovarian, bladder and lung carcinomas. However, their use is limited by severe toxicity including nephrotoxicity, severe gastrointestinal intolerance (with nausea and vomiting), and myelosuppression.

In order to improve the efficacy, as well as to circumvent acquired resistance and/or decrease toxicity, the search for new chemical entities led to the discovery of the diaminocyclohexane (DACH) platinum family in the 1970s. Oxaliplatin (trans-l DACH oxalatoplatinum or L-OHP) was described in 1976 in Japan by Pr. Kidani, and is the first DACH-member to reach the market (Galanski *et al.*, 2004).
On reviewing the literature (search terms: Oxaliplatin AND / OR hearing loss: 1966 to date), there has been only one report of a case of oxaliplatin induced hearing loss. Malhotra (2010) reported unilateral hearing loss in a 70-year-old woman who was undergoing postoperative chemotherapy for rectal adenocarcinoma and had developed hearing loss following a single infusion of Oxaliplatin, which persisted and never recovered.

4.3 Preventing and monitoring ototoxicity

Ototoxicity is the primary dose limiting effect of cisplatin and carboplatin (to a lesser extent) and can be influenced by various factors such as drug administration method, dosage per treatment and accumulated dosage. To date, attempts to reduce the side effects by developing equally potent platinum analogs has proved futile. Some success however has been achieved by co-treatment with protective agents. Most of these agents are sulphur or sulfhydryl containing compounds (thio compounds) known as antioxidants and potent heavy metal chelators. They provide protection against cisplatin ototoxicity in the following ways:-

1 Direct interaction between cisplatin and thio moiety
2 Preventing platinum from interfering with superoxide dismutase
3 Displacing platinum from its site of toxic action
4 Scavenging cisplatin induced free radicals (Smoorenburg *et al.*, 1999)

D- methionine, sulphur containing nucleophile and antioxidant, may protect against cisplatin-induced ototoxicity by chelating the platinum, reversing the cellular platinum –thiol complexes, protecting the essential aminoacid L-methionine or simply functioning as an antioxidant. It does appear to have a fairly generalised protective effect not only against ototoxicity but also against nephrotoxicity (Campbell *et al.*, 1999).
Monitoring the ototoxic effects of cisplatin has also been a topic of discussion.

Fausti (1993) suggested that an effective hearing monitoring protocol should provide the earliest possible detection of hearing loss. The proposed recommendations are conventional audiometry (250Hz to 8000Hz), high frequency audiometry and otoacoustic emissions(OAE). However, the basic audiological assessment is still limited to conventional audiometry. High frequency audiometry, on the other hand, can be employed to detect ototoxic changes caused by cisplatin above 8000 Hz, which corresponds to early cochlear insults. It clearly detects pre-clinical ototoxicity with greater sensitivity than conventional audiometry. (Durant *et al.,* 2009*)*
Knight (2007) evaluated the feasibility of extended high frequency audiometry (EHF; 9 to 16kHz) and distortion product otoacoustic emission (DPOAEs) as a mode for monitoring ototoxicity in patients having platinum based chemotherapy by measuring hearing thresholds using conventional audiometry (0.5 to 8000 kHz) in 32 patients and EHF and DPOAEs in 17 patients. Their results showed that EHF and DPOAEs identified ototoxic changes earlier when compared with conventional audiometry.
Coupland (1991) investigated the usefulness of broadband clicks and derived auditory brainstem evoked response audiometry (ABR) in investigation of early cisplatin ototoxicity by monitoring progressive hearing loss in 18 children undergoing chemotherapy over a two-year period. They concluded that derived ABRs were found to be more sensitive than broadband click ABR in detecting early high-frequency hearing loss.

4.4 Conclusion

Platinum based drugs are invaluable for the treatment of many types of cancer including head and neck but do have serious side effects, of which, hearing loss is one. This can be very debilitating for patients. It is of paramount importance that the ototoxicity occurring as result of these agents is effectively monitored and prevented.

CHAPTER 5

DEAD REGIONS & THRESHOLD EQUALISING NOISE TEST

5.1 Introduction

5.2 Dead Regions

(i) Definition

(ii) Review of literature

(iii) Clinical signs

(iv) Methods of detection

5.3 Threshold equalising noise (TEN) test

(i) Review of literature

(ii) Limitations

5.4 Clinical uses

5.1 Introduction

Sounds entering the ear lead to vibrations of the basilar membrane within the cochlea with high frequencies producing maximal vibration at the base and low frequencies towards the apex of the basilar membrane. The frequency that leads to the maximal vibration at a given place on the basilar membrane is called the characteristic frequency (CF) for that place. Cochlear hearing loss is often associated with damage to the hair cells thereby leading raised hearing thresholds. OHC's injury causes impairment of the active mechanism in the cochlea, which results in reduced basilar membrane. Hence the sound level must be larger than normal to give a just detectable amount of vibration. On the other hand, IHC damage can lead to a less efficient stimulation of the auditory nerve. IHC at certain places along the basilar membrane may be completely non-functioning and the auditory neurons making the connection may be non-functioning. Places with non-functioning IHC's and /or neurons have been referred to as 'dead regions'. A high frequency tone presentation may be detected a region closer to the low frequency (apical end) if it produces sufficient basilar membrane vibration and similarly a low frequency tone may be detected via neurons that are tuned to detect high frequency tone. This in turn leads to the true hearing loss at a given frequency being greater when compared with the audiometric threshold at that frequency.

5.2 Dead Regions

(i) Definition

In regions of the cochlea where Inner Hair Cells (IHC) or their associated neurones are completely non-functional, the transduction process cannot occur; there is no conversion of basilar membrane (BM) vibration into action potentials. Consequently information from BM vibration within that region cannot be passed to the brain; the hearing loss in such regions is effectively infinite. This phenomenon is known as a 'Cochlear Dead Region' (Moore, 2004)

(ii) Review of literature

The extent of a dead region (DR) has previously been defined according to location or distance along the Basilar Membrane, which was non-functioning, for example extending from 0-12mm for a basal dead region (Moore, 2004 ; Moore, 2001). As the cochlea is known to demonstrate frequency-place specificity, a dead region may also be defined by the CF normally associated with that region e.g. extending from 4000 to 1000 Hz (Moore, 2002). When a dead region is present, an audiogram can give misleading information on the extent of the hearing loss, for a tone whose frequency falls in the dead region. The true hearing loss in a dead region is infinite, but an audiogram may only indicate a moderate hearing loss if the frequency of the tone lies close to the boundary of the dead region (Moore, 2004). Halpin (1994) described two patients with low frequency hearing loss on their audiograms. However, on postmortem examination, one had no surviving organ of corti at apical region whereas the other person had normal organ of Corti. Moore (2000) stated that steep sloping audiograms (high frequency hearing loss) are usually associated with dead regions but dead regions can also be linked to a shallow sloping audiogram.

(iii) Clinical signs

The following table illustrates the clinical signs of dead regions.

Clinical signs of a DR	Source
Audiogram slope and severity: (i) Hearing losses of >90dB at high frequencies or 75-80dB at low frequencies (ii) Hearing losses of 40-50dB at low frequencies with near-normal hearing at medium and high frequencies (perhaps indicative of a low-frequency DR) (iii) Hearing losses >50dB at low frequencies with somewhat less hearing loss	Moore (2004) Aazh & Moore (2007) Vinay & Moore (2007)

at higher frequencies (perhaps indicative of a low-frequency DR) And/or: Hearing loss increasing rapidly (more than 50dB/octave) with increasing frequency (perhaps indicative of a high-frequency DR)	
Subjective reports from the patient during PTA that the tones sound noise-like rather than tone like. This often occurs where the pure tone falls well within a DR. Reports of noise-like tones may also occur where there is no DR.	Moore (2004) Huss and Moore (2005) Munro (2007)
Lack of benefit from previously fitted hearing aids	Moore (2004)

Table 5.2(iii): Clinical signs of Dead Regions

(iv) Methods of detection

Whilst BM vibration information arising within a dead region itself is not transmitted to the brain, a tone of frequency falling within a dead region may still be detected. An apical or basal spread of the vibration pattern to adjacent functioning IHCs and neurons of a different CF will result provided the sound is of a sufficient intensity (Moore and Alcántara, 2001). Such detection of a sound is referred to as 'off-frequency' or 'off-place' listening (Moore, 2004). The tests for the detection of dead regions are based upon the occurrence of off-place listening. Many researchers have used masking techniques to establish the presence of dead regions and to approximate their boundaries (Moore and Alcántara, 2001; Summers *et al.*, 2003; Sek *et al.*, 2005). Various tests, which have been used to detect dead regions, include

(i) Traditional Psychophysical Tuning Curves (PTCs)

(ii) Threshold equalizing noise test (TEN)

(iii) Fast Psychophysical Tuning Curves (PTCs)

5.3 Threshold Equalising noise (TEN) test

(i) Review of Literature

Moore (2000) developed a test using an alternative masking technique for detection of dead regions, which avoids the problems associated with PTC (Psychophysical tuning curve). The long test duration of PTCs has also been shortened considerably to roughly twice as long as measurement of a single audiogram; masked thresholds of sinusoids are measured for only of the standard audiometric frequencies in the presence of Threshold Equalising Noise (TEN Test) (Moore *et al.*, 2000; Moore, 2002; Moore, 2004; Kluk and Moore, 2006).

A two-channel audiometer is required to mix and independently adjust the levels of the sinusoid and TEN, which is sourced from a compact disc (CD) upon which it is recorded, and presented to the same ear (Moore, 2002). TEN test is spectrally shaped so that masked thresholds (dB SPL) for normally hearing subjects should be equal for sinusoids between 250-10,000 Hz (Moore *et al.*, 2000).

The test involves measuring the thresholds for detecting a pure tone presented in a background noise called threshold equalising noise. Initially the noise was synthesized in such a way that the threshold for detecting a tone in the noise, specified in dB SPL, was approximately the same for all tone frequencies in the range 250Hz to 10Hz, for people with normal hearing. However, a problem with this original version of TEN test for the clinician was the fact that he had to measure absolute threshold (audiometric threshold) twice, once using the tones generated by the audiometer with level specified in dB HL and once using the tones from TEN test CD with level specified in dB SPL. In order to overcome this, a new version was designed in which the noise gave equal masked thresholds in dB HL for all frequencies from 500 to 4000Hz for normally hearing individuals. As all the calibrations are in dB HL, absolute thresholds can be measured either using the tones generated by the audiometer or using the test tones from the CD, the results would be similar.

(ii) Rationale behind TEN test

The rationale behind the TEN test involves measurement of threshold for detecting a pure tone noise in the background of a masking noise. A pure tone signal, when presented to the ear, is detected by fully functioning inner hair cells on the basilar

membrane frequency leading to a response. The introduction of a background noise does not lead alteration of the thresholds on masking as there are fully functioning inner hair cells on the basilar membrane. However on the other hand, when there are no functioning hair cells on the basilar membrane, a pure tone signal falling in the area of the dead region leads to less then sufficient basilar membrane vibration. This is due the fact this pure tone signal is now being picked by remote areas on the basilar membrane where there are some functioning IHC's. The amount of vibration produced as a result at this remote region will be less than in the dead region and thereby the masking the noise will be very effective in masking it as well as any off peak frequency listening and hence more accurate thresholds.

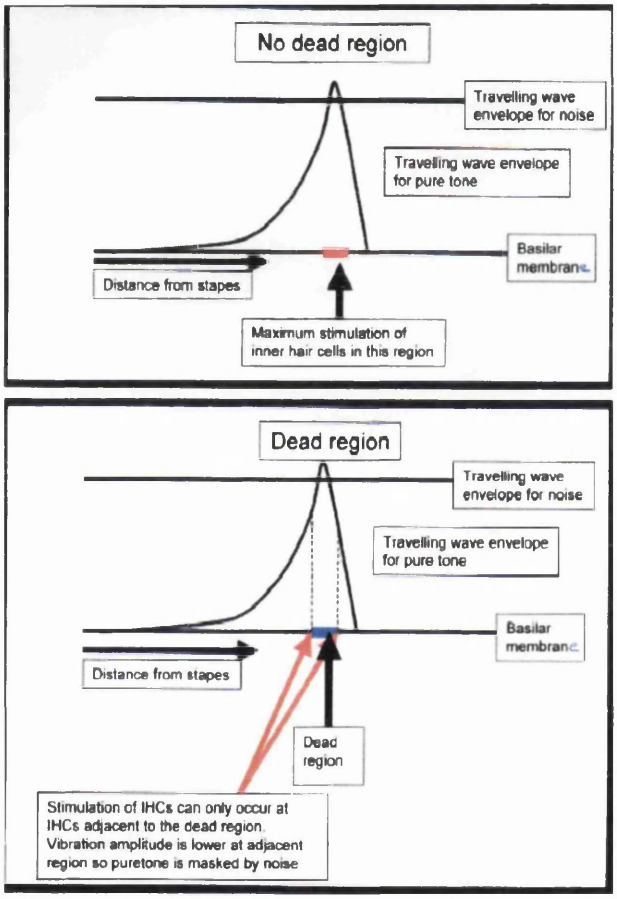


Figure 5.3 (ii) Travelling wave & dead region (Meredith, 2010- personal communication)

Additionally, TEN used with the dB (HL) version has a restricted bandwidth (now 354-6,500 Hz, as opposed to the 250-10,000 Hz range of the original TEN), producing almost equal masked thresholds between 250 Hz -4 KHz. This enables the masker level to be increased whilst avoiding the complications of distortion,

excessive loudness and possible noise-induced damage to hearing (Moore *et al.*, 2004). The TEN (HL) test is therefore more efficient and faster than its predecessor. As with the original TEN test, frequencies falling within a dead region are identified by masked thresholds that exceed the absolute threshold by at least 10 dB and also a minimum 10 dB above the level/ERB of TEN used (Moore *et al.*, 2004).

Whilst in clinical audiology it is standard practice to measure thresholds within 5 dB, Moore (2004) suggests a step size of 5 or 10 dB to approximate the level of masked threshold, then a smaller step size of 2 dB to determine it more precisely. He also acknowledges the limited accuracy of both versions of the TEN test; the test frequencies used on the CD necessary to perform the test are spaced at one-half octave intervals, inherently limiting precision of the test in determining f_e (Dead region edge frequency)

Cairns (2007) investigated short-term test-retest repeatability of the TEN (HL) test (between 0.5-4kHz) for 15 teenagers with long-standing severe-to-profound sensorineural hearing loss (SNHL), and 20 adults with moderate-to-severe SNHL, by repeating the TEN (HL) test within five days using the same equipment. They concluded that less than 5% of ears tested for both groups changed category at individual frequencies, with the exception of 1.5 and 4 kHz. Most ears that changed category only just met dead region criteria. Markessis (2006) reviewed 24 subjects with normal hearing and 35 patients with steeply sloping high-frequency for the effect of high-pass filtering on the TEN-test results and the loudness of the TEN. They used the standard TEN (TENs), and TEN high-pass filtered at 0.5 kHz (TEN0.5) or 1 kHz (TEN1). The TEN1 was found to be the most comfortable noise by 68% of the hearing-impaired subjects and concluded that high-pass filtering would allow testing at higher TEN levels for patients with steeply sloping hearing loss.

(iii) Limitations

The original TEN test measured levels in dB (SPL) resulting in clinicians measuring thresholds twice, once in dB (HL) then in dB (SPL). Actual levels of sound for both the masker and sinusoid presented to the test subject were not as indicated by the audiometer; the masker being 10dB(SPL) lower whilst the test tone (also sourced from the CD) was 10dB(SPL) higher (Moore, 2002). There was difficulty achieving

valid results for those with severe or profound hearing loss (Moore *et al.*, 2003). Moore (2004) have attributed this to three main reasons:

(i) Insufficient levels of masking to raise the masked threshold by 10dB or more above the absolute threshold due to excessive loudness (thus inconclusive results obtained).

(ii) Avoiding potentially damaging noise levels.

(iii) Limitations of the audiometer.

Moore (2004) argued that structural abnormalities within the test cochlea might result in the TEN test criteria being met due to a resultant absence of residual frequency selectivity. This will cause only slightly less BM vibration at the point the signal is detected compared to its peak that falls within the DR.

Moore (2004) developed a new version of the TEN test, which expresses all levels in dB (HL) rather than dB (SPL), allowing clinicians to measure absolute thresholds once. Furthermore, the likelihood of errors is reduced by this new procedure as the calibration is such that both TEN level/ERB and the test tone levels correspond to those displayed by the audiometer in dB (HL), aiding interpretation of results.

5.4 Clinical uses

The various clinical uses of the TEN test could be enumerated as follows:

(i) The presence or absence of dead regions can have important implications for fitting hearing aids and for predicting the likely benefit of hearing aids.

(ii) The test may also be useful in selecting candidates for novel forms of hearing aids, such as those incorporating frequency transposition or frequency compression.

(iii) The results from TEN test can be used to assess candidacy for cochlear implant and in medico-legal work. (Moore *et al.*, 2004)

CHAPTER 6

METHODOLOGY

6.1 Introduction

6.2 Methods

6.3 Study design

6.4 Study Population

6.5 Clinical examination

6.6 Environment and procedure

(i) Audiometer
(ii) Pure tone audiometry
(iii) Threshold equalising noise (TEN) test

6.1 Introduction

The present study evaluated patients undergoing platinum based chemotherapy for presence of dead regions within the cochlea using TEN HL (threshold equalising noise) test.

6.2 Methods

This thesis was undertaken after full ethical approval was granted from the South West Wales Local Research Ethics Committee. (Ref: 05/WMW02/68)

6.3 Study Design

Patients due to have platinum based chemotherapy (Cisplatin, Carboplatin or Oxaliplatin) at the chemotherapy day unit at Singleton hospital, Swansea were contacted before commencing their chemotherapy, informed about the study and invited to participate. All volunteers were provided with a copy of the patient information leaflet to read and, if they agreed to take part in the study, were asked to sign a consent form. The clinical investigator, Mr. Sandeep Berry, took a short clinical history. Patients recruited onto the study were asked to attend the Audiology department at Singleton hospital, Swansea to take the TEN (HL) test at a convenient time. The study was carried out over a period of 24 months.

6.4 Study Population

Fifty patients awaiting chemotherapy with platinum based drugs at Chemotherapy day unit, Singleton hospital, Swansea were recruited and their hearing assessed by threshold equalising noise (TEN HL) test for the presence of dead regions before initiation of therapy and then at 1, 6 & 12 months post treatment. A note of the drug dosage was made but no attempt was made to correlate platinum drug dosage with dead regions, as this did not constitute a part of the present study.
All patients recruited satisfied the inclusion and exclusion criteria for the study (listed below)

Inclusions:

- Age 20-75 years, both male and female patients
- On chemotherapeutic agents (cisplatin, carboplatin and oxaloplatin)

Exclusions:

- Middle or outer ear disease causing conductive hearing loss
- On other ototoxic drugs (past or present)
- Congenital hearing loss
- Patients who do not, or are unable to, consent to the trial
- Terminally ill patients

6.5 Clinical Examination

Patients who were recruited for the study underwent otoscopic examination prior to undergoing pure tone audiometry and TEN (HL) test, neither of which were invasive. The tests were done before and after treatment as per protocol.

6.6 Environment and procedure

Testing room, Audiology department

The testing was carried out in a sound proof room within the Audiology department at Singleton hospital. The subject was informed about the procedure (PTA & TEN test) in detail and was given ample opportunity to ask questions. An otoscopic examination

was done prior to PTA and TEN (HL) test to exclude any wax or infection. Pure tone audiometry was initially performed, followed by TEN (HL) test.

(i) Audiometer

A two-channel audiometer with CD player (GRASON-STADLER; GSI61) was used for the PTA and TEN tests.

(ii) Pure Tone Audiometry

Subject was asked to sit on a chair facing away from the audiometer, in a manner to promote safety and comfort as well as valid testing. The details of the testing procedure were fully explained to the subject and every effort made to ensure that they understood them properly. Headphones (TDG 49) were put on the subject's head and a button given to them to press when they heard the sound. Air conduction thresholds were tested for frequencies from 500 Hz to 8 KHz, including 750 Hz, 1.5 KHz & 3 KHz, for both ears. The results were plotted on the audiometry chart. If there was a significant difference between air conduction thresholds between two ears, then rule of masking were applied and thresholds re-tested and recorded.
The rules of masking used are as follows:
Rule 1: Masking was employed where the difference between the left and right not-masked air conduction thresholds is 40 dB
Rule 2: Masking will be needed additionally where Rule 1 has not been applied, but where the bone conduction threshold of the better ear is more acute by 40 dB (if supra or circum-aural earphones have been used) or 55 dB (if insert earphones have been used) or more than the not-masked air conduction threshold attributed to the worse ear.

(iii) Theshold equalising noise test (TEN HL)

Following the PTA, TEN test was carried out using a CD, containing noises for frequencies (500 Hz, 750 Hz, 1000 Hz, 1500 Hz, 2000 Hz, 3000 Hz & 4000 Hz). A two-channel audiometer with CD player was used for this purpose. The test noise was initially calibrated prior to testing. TEN (HL) test was carried out as per the instructions on the test CD (see below)

(ii) All the cables from CD player to Audiometer were plugged in.

(iii) Left Output from CD player (A) was fed into left input on the audiometer with right output from CD player (B) into right input on the audiometer.

(iv) Left (A) input for channel 1 on the audiometer and right (B) input for channel 2 on the audiometer was selected.

(v) Calibration was performed by playing Track 1 on the CD and setting the audiometer so that both line inputs are continuous (interrupt button on the audiometer on), and adjusting VU meters on the audiometer to read 0dB.

(vi) The two channels were mixed and directed to right ear first with desired noise level controlled using channel 1.

The thresholds (masked) for each frequency for the right ear were measured and recorded using Tracks 2-8 on the TEN (HL) CD while playing the noise continuously (interrupt button on the audiometer for channel 1 pressed). The test tone was delivered from channel 2 on the audiometer.

(vii) The TEN (HL) threshold was set at 10dB above the level of the audiometric threshold for all the frequencies to be tested.

(viii) The above step was repeated for the left ear.

A dead region at a particular frequency was indicated by a masked threshold that was at least 10dB above the absolute threshold and 10 dB above the nominal noise level. If a dead region was detected for a particular frequency, the absolute threshold was re-measured using 2dB increments.

CHAPTER 7

RESULTS

7.1 Introduction

7.2 Demographics

7.3 Results

(i) Type of platinum drugs

(ii) Patient Data

(iii) Patients who completed 12 months (group A)

(iv) Patients who completed 6 months (group B)

(v) Patients who completed 1 month (group C)

(vi) Patients who only had pre chemotherapy testing (group D)

7.4 Important observations

7.5 List of patients with dead regions

7.1 Introduction

This was a longitudinal study on a group of 50 patients having chemotherapy with platinum chemotherapeutic drugs (Cisplatin, Carboplatin & Oxaliplatin) who were assessed for the presence of dead regions before initiation of therapy and then at 1, 6 & 12 months post treatment using the threshold equalising noise (TEN HL) test.

7.2 Demographics

Fifty patients were included in the present study.

a. Male: 26
b. Female: 24

The age range was 20- 75 years.

The mean age was 58.8 years and the median age was 60 years

AGE	MALE	FEMALE
20-40	3	2
41-50	2	4
51-60	9	7
61-70	6	6
71-75	6	5

7.2: Patient distribution

7.3 Results

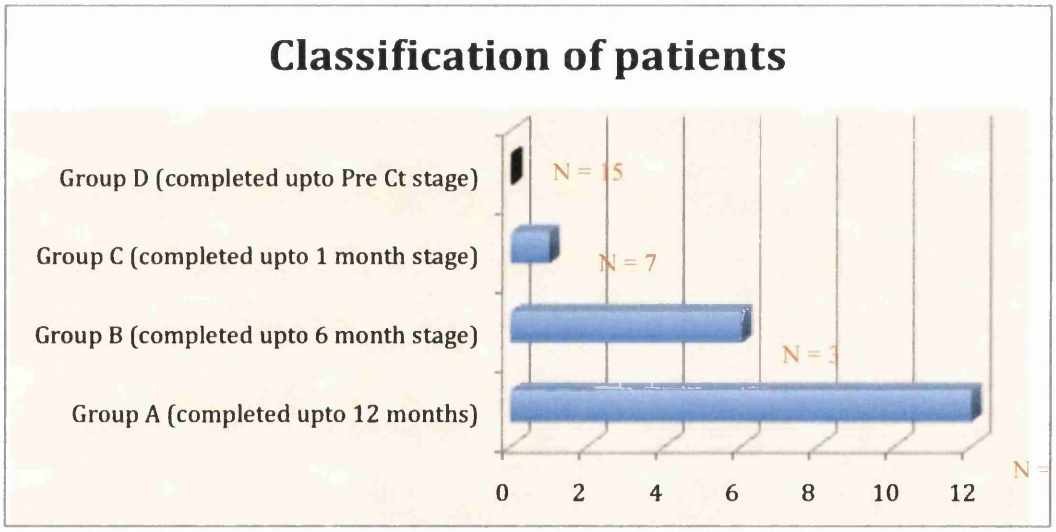
(i) Type of platinum drugs

The following table illustrates the patient age groups versus type of platinum drug they received.

AGE (Years)	CISPLATIN	CARBOPLATIN	OXALIPLATIN
20-40	5	0	0
41-50	3	1	2
51-60	7	7	2
61-70	3	5	4
71-75	1	7	3
TOTAL	19	20	11

7.3 (i): Patient age groups versus type of platinum drug they received

(ii) Patient data



7.3 (ii): Patient classification versus various groups

(iii) Patients who completed 12 months of the study (group A)

Twenty-five patients completed the whole study, which included TEN testing prior to chemotherapy and then one, six and twelve months post chemotherapy. Out of the 25 patients, 21 patients (84%) showed no evidence of dead regions on TEN (HL) test at the end of the study.

Four patients out of the 25 (16%) showed evidence of dead regions at various intervals of the study with all cases highlighted individually below.

AGE	FREQ OF DR	PRE CT	1/12	6/12	12/12	DRUG
74/m	3KHz	N	N	N	Y; LE	Oxaliplatin
66/m	3KHz	N	N	N	Y; LE	Carboplatin
58/m	3KHz 4KHz	N N	Y; LE Y; LE	N N	N N	Cisplatin
74/m	4KHz	Y; LE	N	N	Y; RE	Oxaliplatin

Y; RE = dead region in right ear

Y; LE = dead region in left ear

DR = dead region

CT = Chemotherapy

7.3 (iii): Patients who completed 12 month of study (Group A)

(iv) Patients who completed 6 months (group B)

Three patients (6%) completed the study up to the stage of TEN testing at six months post chemotherapy. Two out of the three patients showed evidence of dead regions on TEN testing at 6 months, but all three patients passed away prior to their twelve months TEN testing.

AGE	FREQ OF DR	PRE CT	1/12	6/12	12/12	DRUG
69/m	4KHz	N	N	Y; RE	Died	Oxaliplatin
60/m	3KHz 4KHz	N N	N Y; RE	Y; LE Y; RE	Died	Carboplatin / Cisplatin

Y; RE = dead region in right ear

Y; LE = dead region in left ear

DR = dead region

CT = Chemotherapy

7.3 (iv): Patients who completed up to 6 months stage of the study (Group B)

(v) Patients who completed 1 month (group C)

Seven patients (14%) completed the study up to the stage of TEN testing at one month post chemotherapy. Five patients opted out of the study due to ill health and two patients passed away. Six out of the seven patients did not reveal any dead regions but one showed the presence of dead region on TEN testing.

AGE	FREQ OF DR	PRE CT	1/12	6/12	12/12	DRUG
75/f	750Hz	N	Y; LE	Opted out	------	Carboplatin

Y; LE = dead region in left ear

DR = dead region

CT = Chemotherapy

7.3 (v): Patients who completed up to 1month stage of the study (Group C)

(vi) Patients who only had pre chemotherapy testing (group D)

A total of fifteen patients (30%) completed the study up to the stage of TEN testing prior to commencement of chemotherapy. Seven patients opted out of the study due to ill health and eight patients passed away. Thirteen out of the fifteen patients did not reveal any dead regions but two showed the presence of a dead region on TEN testing.

AGE	FREQ OF DR	PRE CT	1/12	6/12	12/12	DRUG
72/f	4KHz	Y; LE	Died	----	-------	Carboplatin
43/f	1KHz 1500Hz 2KHz	Y; RE Y; BE Y; RE	Opted out	----	-------	Carboplatin

Y; RE = dead region in right ear

Y; BE = dead region in both ears

Y; LE = dead region in left ear

DR = dead region

CT = Chemotherapy

7.3 (vi): Patients who completed up to Pre chemotherapy stage of the study (Group D)

7.4 Interesting observations

A few interesting observations were recorded during the present study. These are presented below:

(i) The timing of sensorineural hearing loss for each of the drugs used was noted. Hearing loss was defined as a worsening of the threshold by more than 10 dB HL at 500 Hz, 1KHz, 2KHz & 4KHz.

Cisplatin (n= 8)

The primary frequency involved was 8KHz.

	Right Ear	Left Ear	Both
Pre CT			1
Post CT 1/12	1	2	1
Post CT 6/12	1	1	
Post CT 12/12	1		

7.4 (i) a: Timing of SNHL & Cisplatin

Carboplatin (n = 8)

The primary frequency involved was 8KHz but one patient also had sensorineural hearing loss at 4KHz.

	Right Ear	Left Ear	Both
Pre CT	1	1**	1** + 3
Post CT 1/12	1*		
Post CT 6/12	1		
Post CT 12/12	1		

7.4 (i) b: Timing of SNHL & Carboplatin

1** = Patient had SNHL at Pre- CT at 500hz /1K/ 2K & 4KHz in both ears and in left ear at 8K

1* = Patient had SNHL at 4KHz at 6/12 post CT in left ear and at 8KHz in left ear at 1/12 post CT

Oxaliplatin (n = 6)

The primary frequency involved was 8KHz.

	Right Ear	Left Ear	Both
Pre CT		1	1
Post CT1/12	1**	1*	
Post CT 6/12		2	
Post CT 12/12	1*		

7.4 (i) c: Timing of SNHL & Oxaliplatin

1* = Patient had SNHL at 1/12 post CT in left ear and 6/12 post CT in right ear.

1** = Patient had SNHL at 1/12 post CT in right ear.

(ii) The timing of the occurrence of the dead regions was reviewed for the various groups of patients. These cases will be highlighted in the discussion.

Group A: Completed 12/12

				Hearing Threshold (dB HL)		
Patient	Drug	Timing of DR	Ear	Time of DR	Pre CT	Frequency
1.	Oxaliplatin	12/12 post CT	Left	55	35	3KHz
2.	Oxaliplatin	12/12 post CT	Right	80	60	4KHz
3.	Cisplatin	1/12 post CT	Left	65	45	3KHz
	Cisplatin	1/12 post CT	Left	95	70	4KHz
4.	Carboplatin	12/12 post CT	Left	65	50	3KHz

Group B: Completed 6/12

				Hearing Threshold (dB HL)		
Patient	Drug	Timing of DR	Ear	Time Of DR	Pre CT	Frequency
5.	Cisplatin	6/12 post CT	Left	70	65	3KHz
	Cisplatin	1/12 post CT	Right	55	50	4KHz
6.	Oxaliplatin	6/12 post CT	Right	90	55	4KHz

Group C: Completed 1/12

				Hearing Threshold (dB HL)		
Patient	Drug	Timing of DR	Ear	Time Of DR	Pre CT	Frequency
7.	Carboplatin	1/12 post CT	Left	40	30	750Hz

(iii) Five patients revealed evidence of dead regions on TEN testing at pre - chemotherapy stage. In two patients, the dead region improved at 1/12 post CT, while in one patient the dead region persisted up to 12/12 post CT. The remaining two patients passed away prior to the next stage of testing. None of the five patients had any previous history of chemotherapy with platinum based drugs, loud noise exposure, radiotherapy or use of any ototoxic drug.

Patient	Drug	Ear	Hearing Threshold (dB HL) at the time of DR	Frequency
1.	Carboplatin	Right Right Left Right	80 85 75 75	1KHz 1500HZ 1500HZ 2KHz
2.	Carboplatin	Left	50	4KHz
3.	Oxaliplatin	Left	60	4KHz
4.	Carboplatin	Left	75	4KHz
5.	Carboplatin	Right	85	4KHz

7.4 (iii): Patients with dead region at Pre CT stage versus drugs

(iv) Dead regions were identified in 7 patients at different stages of TEN testing. The variability of the occurrence of the dead regions was an important observation made during this study.

Patient	Timing of DR	Drug	Associated Factors
1.	12/12 post CT	Oxaliplatin	None
2.	12/12 post CT	Carboplatin	None
3	1/12 post CT	Cisplatin	None
	1/12 post CT	Cisplatin	None
4.	12/12 post CT	Oxaliplatin	None
5.	1/12 post CT	Cisplatin	Patient also received carboplatin
	6/12 post CT	Cisplatin	
6.	6/12 post CT	Oxaliplatin	None
7.	1/12 post CT	Carboplatin	None

7.4 (iv): Dead region occurrence & variability

(v) 3 patients in total were noted to have dead regions at different stages of the TEN testing, of which 2 patients had this finding at pre CT stage, while in the remaining 1 subject it, was at 1/12 post CT. In all three, the dead regions resolved spontaneously at the next stage of testing. Hearing thresholds at the time of occurrence and disappearance of dead region were noted.

			Hearing Threshold (dB HL)				
Age/ Sex	Drug	Ear	DR Present	DR absent	DR Present	DR Absent	Frequency
74/M	Oxaliplatin	Left	Pre CT	1/12	60	80	4KHz
58/M	Cisplatin	Left	1/12	6/12	65	50	3KHz
		Left	1/12	6/12	95	70	4KHz
66/M	Carboplatin	Left	Pre CT	1/12	75	70	4KHz

7.4 (v): Spontaneous resolution of dead region versus drugs

(vi) Three patients who received Oxaliplatin showed presence of dead region on TEN testing at six months (n=1) and twelve months (n=2) respectively. In one subject, dead region was observed at pre chemotherapy testing but resolved at the time of one month post chemotherapy testing. On reviewing the literature (search term: Oxaliplatin AND / OR hearing loss: 1966 to date) , there has been no report of any case of oxaliplatin induced hearing loss.

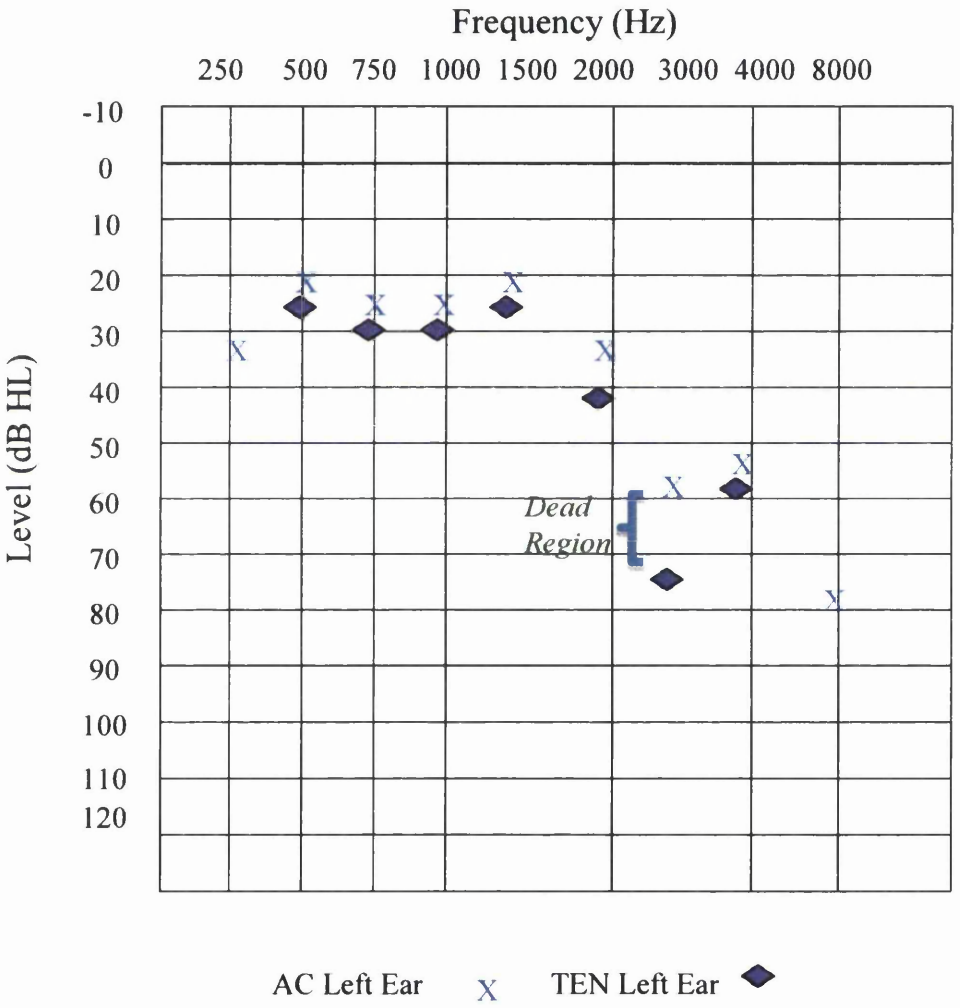
				Hearing Threshold (dB HL)		
Patient	Age/Sex	Timing of DR	Ear	Time of DR	Pre CT	Frequency
1.	69/M	1/12 post CT	Right	90	55	4KHz
2.	74/M	12/12 post CT	Right	80	60	4KHz
3.	74/M	12/12 post CT	Left	55	35	3KHZ

7.4 (vi): Patients who received Oxaliplatin & dead regions

7.5 List of patients with dead regions: section 7.4 (ii)

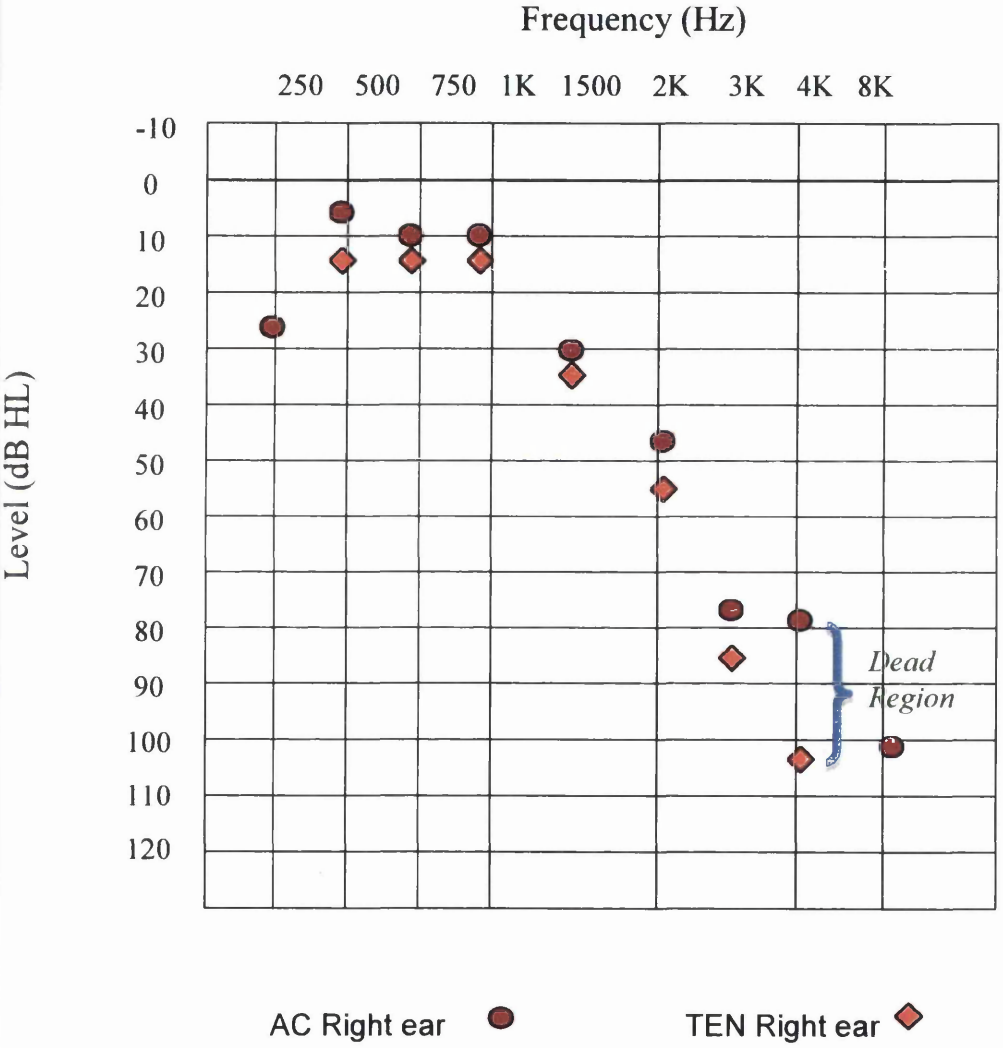
Case 1:

74 year old gentleman who underwent chemotherapy with Oxaliplatin post surgical excision of his bowel cancer, showed evidence of dead region at 3000 Hz at twelve month testing post chemotherapy in his left ear. He had six cycles of chemotherapy and his threshold (dB HL) prior to commencement of chemotherapy was 35 and at time of dead region was 55.



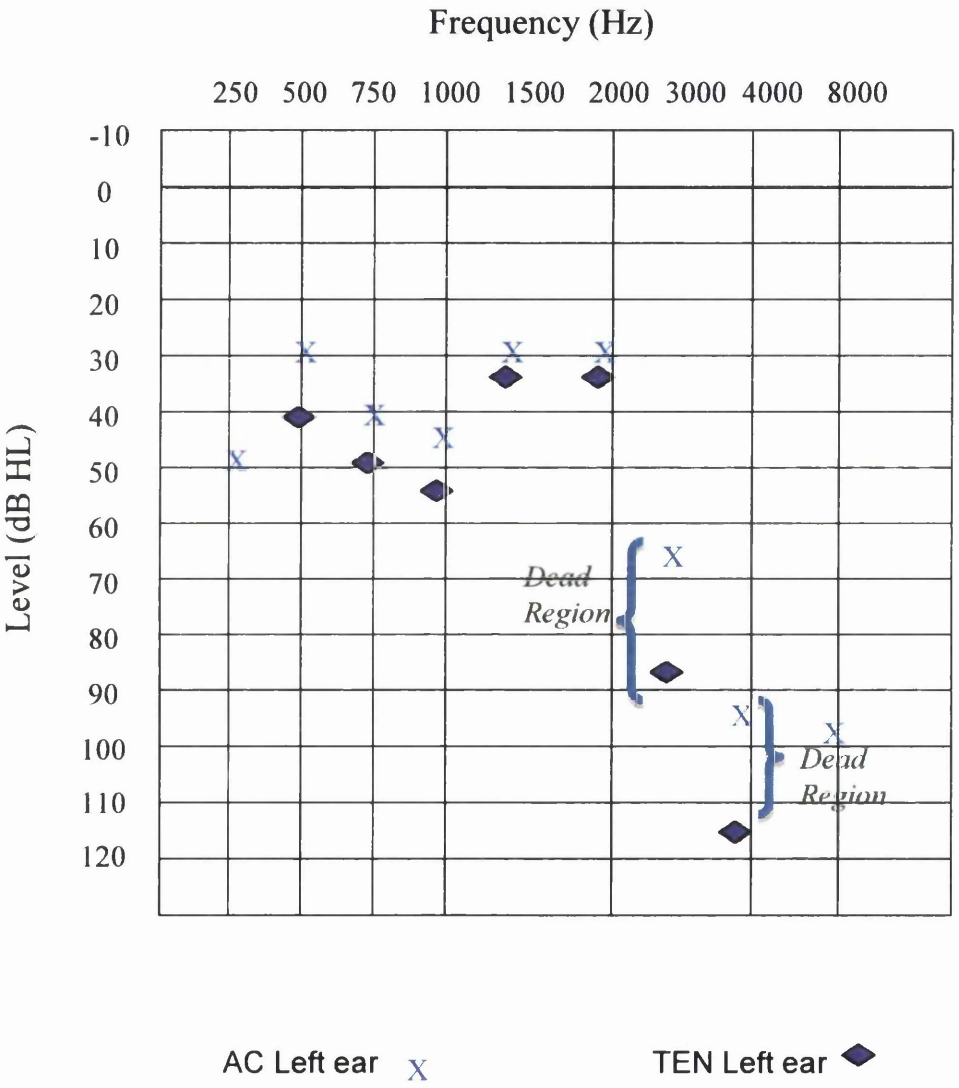
Case 2:

74-year-old gentleman, who underwent chemotherapy with Oxaliplatin post surgical excision of his bowel cancer, showed evidence of dead region at 4000 Hz at twelve-month testing post chemotherapy in his right ear. He had seven cycles of chemotherapy along with capecitabine and his threshold (dB HL) prior to commencement of chemotherapy was 60 and at time of dead region was 80.



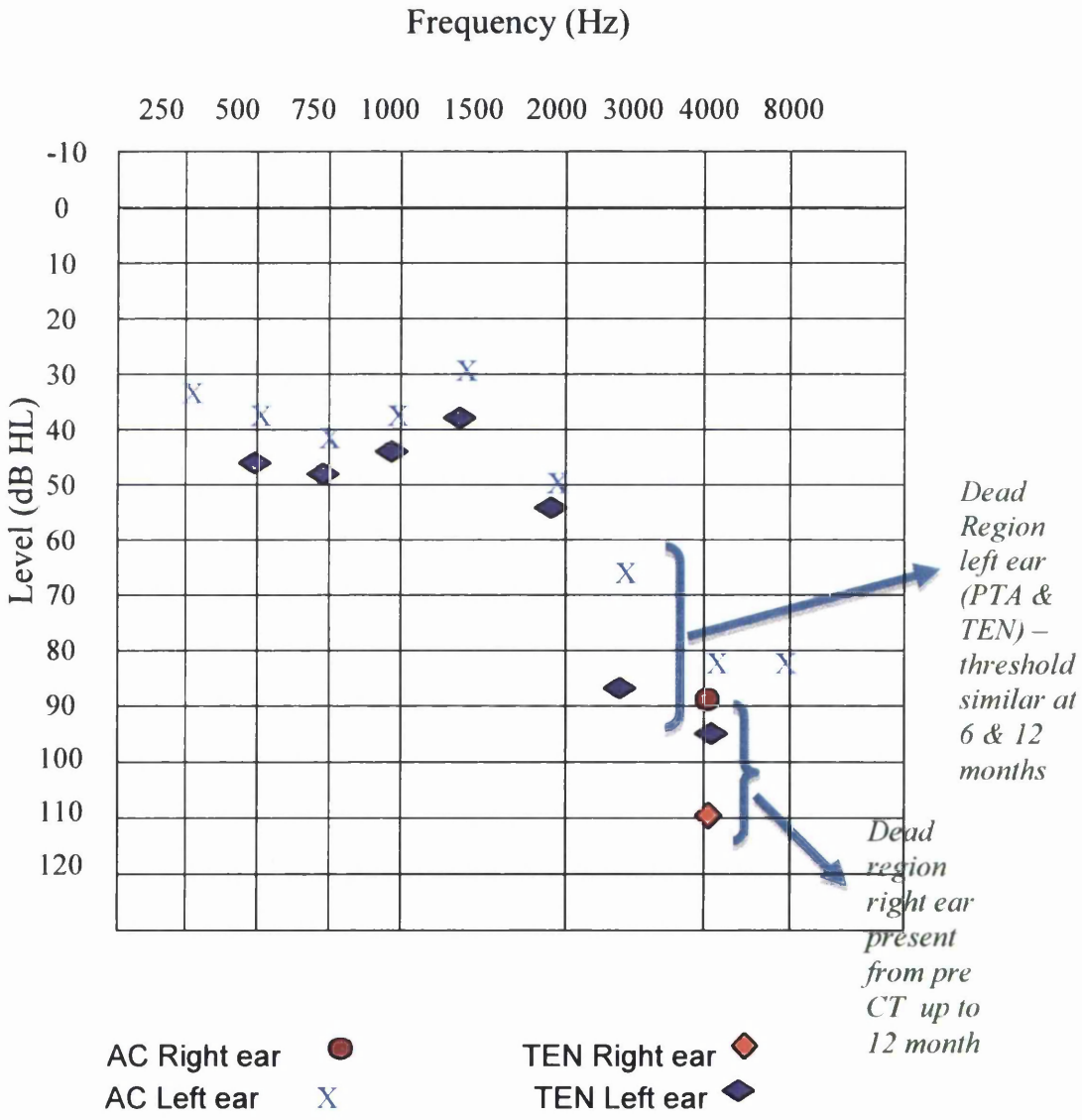
Case 3:

58-year-old gentleman, who underwent chemotherapy with Cisplatin post surgical excision of his laryngeal cancer, showed evidence of dead region at 3000 & 4000 Hz at one month testing post chemotherapy in his left ear. He had five cycles of chemotherapy and his threshold (dB HL) prior to commencement of chemotherapy was 45 & 70 and at time of dead region was 65 & 95 respectively.



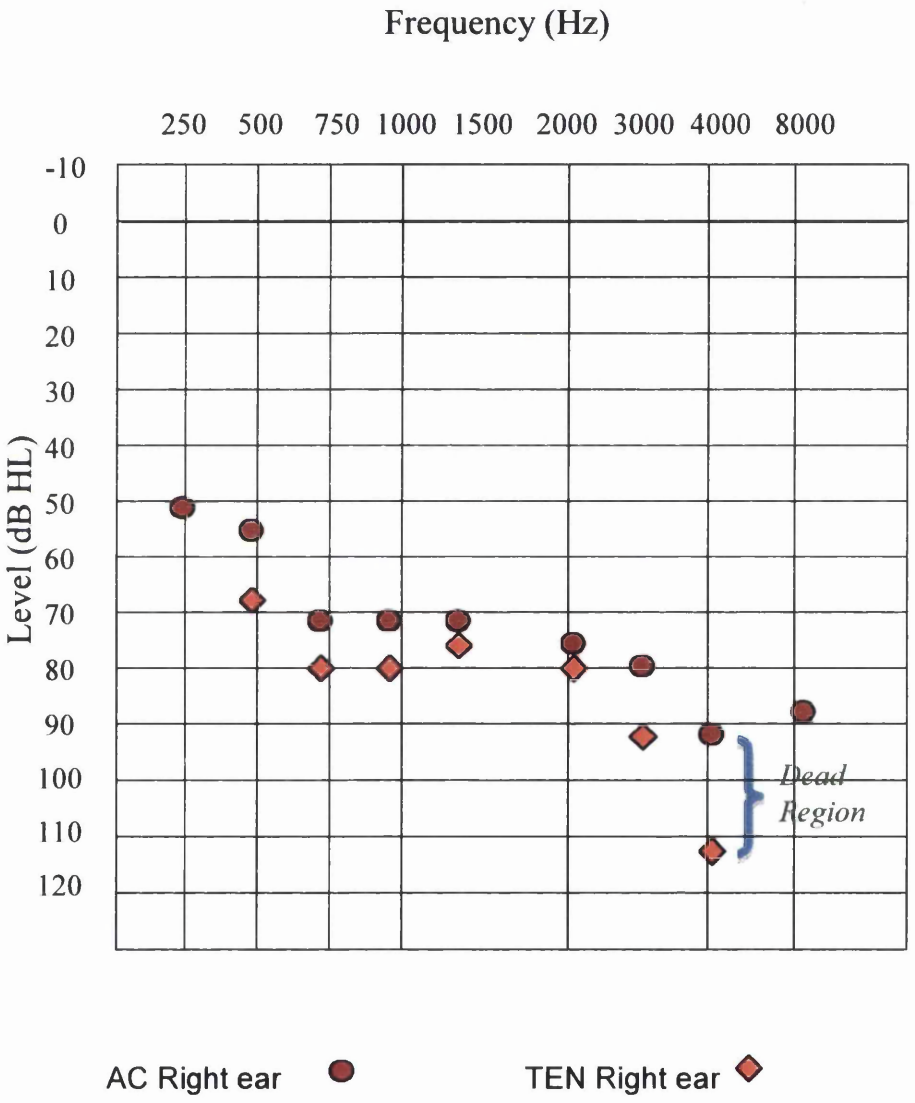
Case 4:

66 year old gentleman, who underwent chemotherapy with carboplatin for recurrent lung cancer, showed evidence of dead region at 3000 Hz at six and twelve month testing post chemotherapy in his left ear. He had four cycles of chemotherapy along with radiotherapy and his threshold (dB HL) prior to commencement of chemotherapy was 55 and at time of dead region was 65



Case 5:

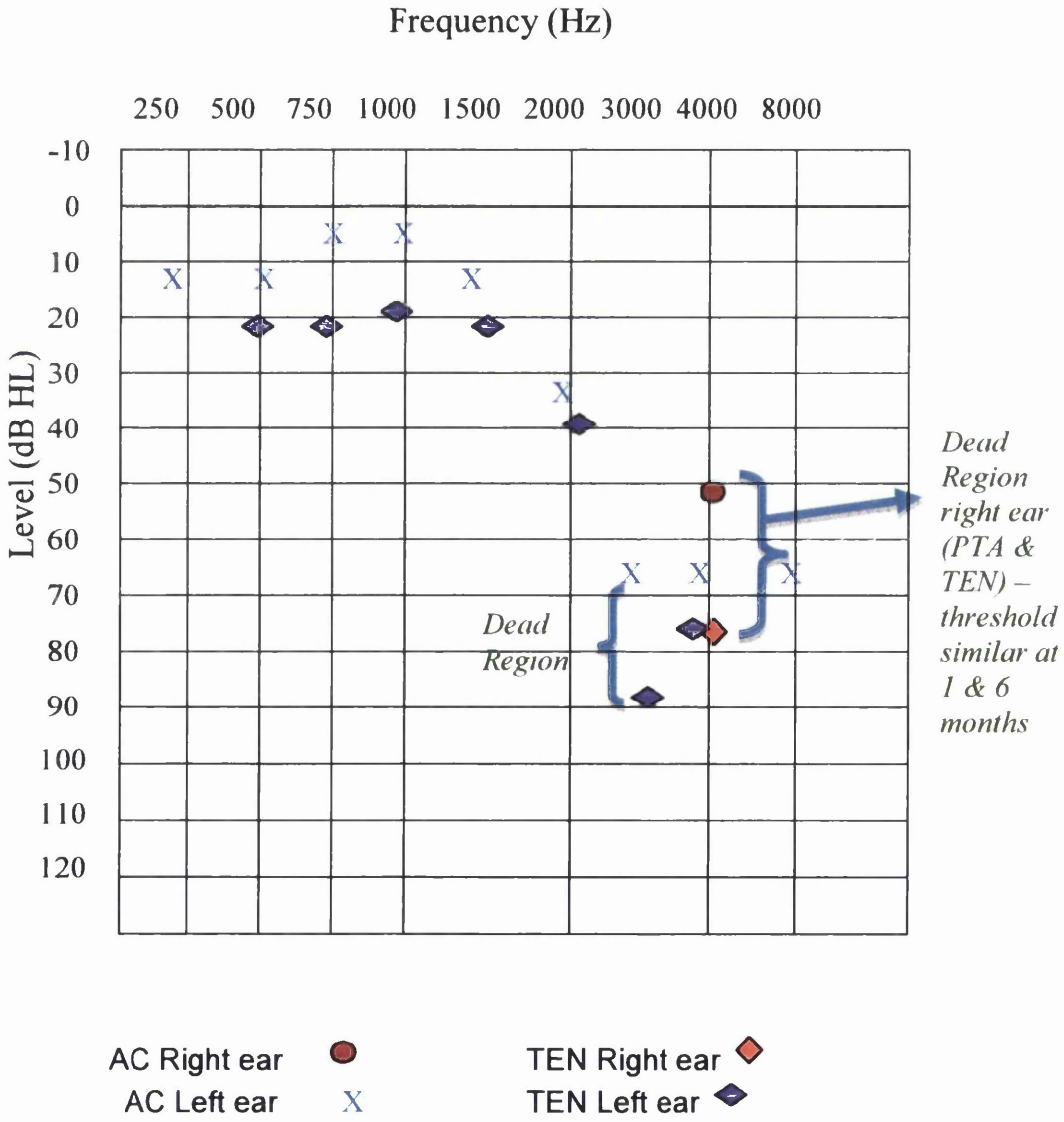
69-year-old gentleman presented with metastatic bowel cancer and underwent extended hemicolectomy followed by three cycles of chemotherapy with Oxaliplatin. Dead region was found at six month testing in his right ear at 4000 Hz. The threshold at pre chemotherapy testing was 45dB HL and at the time of dead region was 90 dB HL. He passed away prior to his twelve-month testing.



Case 6:

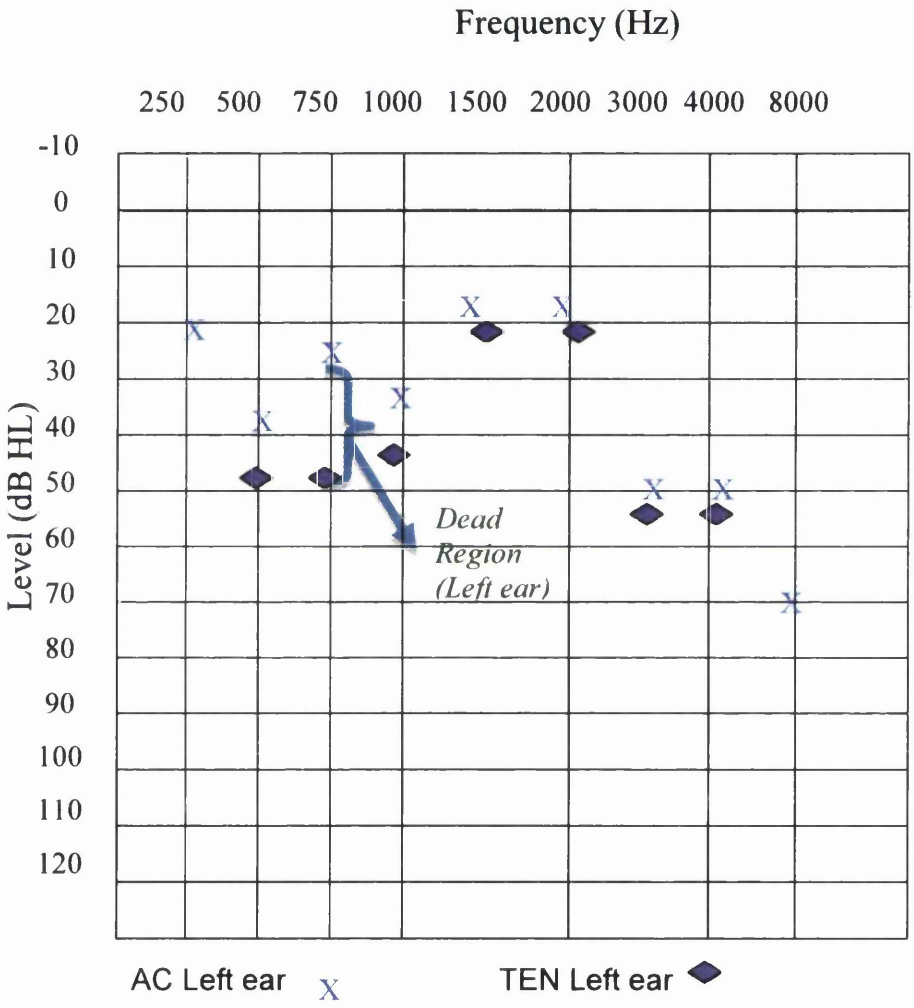
60-year-old gentleman with advanced lung cancer and had chemotherapy with cisplatin (3 cycles) and carboplatin (4 cycles).

He developed dead region at one-month post chemotherapy testing in his right ear at 4000 Hz, which persisted at six-month testing stage. The threshold at pre chemotherapy testing was 50 dB HL and at the time of dead region was 55 dB HL. He also had dead region in his left ear at six-month post chemotherapy stage testing at 3000 Hz and the threshold at pre chemotherapy testing was 65dB HL and at the time of dead region was 70 dB HL. He passed away prior to his twelve-month testing.



Case 7:

75-year-old lady, who had ovarian cancer, underwent debulking and chemotherapy with carboplatin (six cycles). She developed dead region in her left ear at 750Hz at one month post chemotherapy stage testing. She opted out of the study due to ill health and hence was not tested at six and twelve months post chemotherapy. Her threshold in the left ear pre chemotherapy and at time of dead region was 40dB HL.



CHAPTER 8

DISCUSSION

8.1 Introduction

8.2 TEN test and dead regions

(i) Background

(ii) Timing & variability of occurrence

(iii) Presence at pre chemotherapy stage

(iv) Spontaneous resolution

(v) Oxaliplatin & dead regions

8.3 Limitations

8.4 Future implications

8.5 Further research

8.6 Conclusion

8.1 Introduction

A prospective longitudinal study to identify the presence of dead regions in the cochlea of patients who had chemotherapy with platinum based drugs using TEN test was conducted. Fifty patients having chemotherapy with platinum chemotherapeutic drugs (Cisplatin, Carboplatin & Oxaliplatin) were recruited and their hearing assessed by Pure Tone Audiometry and TEN (HL) test for the presence of dead regions before initiation of therapy and then at 1, 6 & 12 months post treatment.
Inclusion criteria have been discussed above.

8.2 TEN test and dead regions

(i) Background

Regions in the cochlea with no or very minimal functioning inner hair cells are termed Dead regions. The fundamental basis of these regions has been mentioned in the literature. Schuknecht (1993) after extensive work on the temporal bones of people with hearing loss, showed that there could be an association between hearing loss and damage to inner and outer hair cells. Discrimination of the sounds, including speech, may be affected when the loss of inner hair cells exceeds 50%.
The extent of a dead region has previously been defined according to non-functioning location or distance along the BM, for example extending from 0-12 mm for a basal dead region (Moore, 2001; Moore, 2004). As the cochlea is known to demonstrate frequency-place specificity, a dead region may be defined by characteristic frequency normally associated with that region, e.g. extending from 4,000 to 10,000 Hz (Moore *et al.*, 2000). Moore (2001) later identified a weakness in this definition: damage to OHCs, often associated with IHC loss, may generate shifts in the characteristic frequency along the BM, causing the characteristic frequency to move relative to their normative values. He devised an alternative definition incorporating these changes; "a dead region is defined in terms of the characteristic frequencies of the IHCs and/or neurons immediately adjacent to the dead region" (Moore, 2001). This new definition simplifies analysis of dead region boundaries when performing psychophysical tests (Moore, 2001).
Whilst basilar membrane vibration information arising within a dead region itself is not transmitted to the brain, a tone of frequency falling within a dead region may still

be detected. An apical or basal spread of the vibration pattern to adjacent functioning IHCs and/or neurons of a different characteristic frequency will result provided the sound is of a sufficient intensity (Moore and Alcántara, 2001). Such detection of sounds is referred to as off-place or off-frequency listening (Moore, 2004). For example, where a dead region starts at 1KHz and extends above this frequency along the basilar membrane, sufficiently intense tones of between 1.0 KHz-1.5 KHz will be detected due to a downward spread of vibration to healthier basilar membrane locations tuned to just below 1 KHz (Moore, 2004).

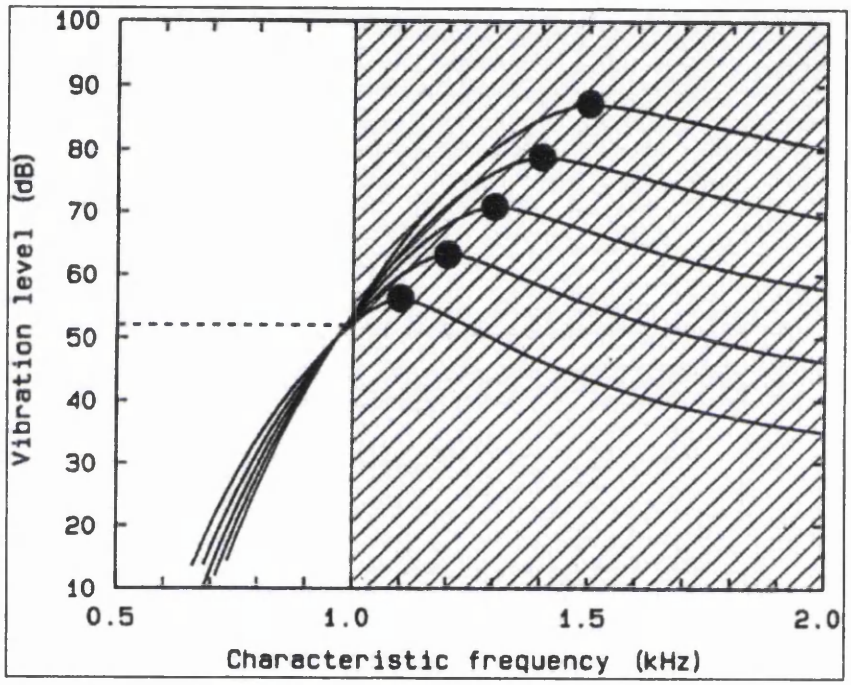


Figure 8.2 (i) Envelopes of BM vibration patterns are illustrated for a hypothetical ear with a DR extending from 1KHz upwards (indicated by the shaded area) and moderate low-frequency hearing loss (the horizontal dashed line represents threshold vibration level): Moore 2004, p. 99

Moore (2004) further identifies that where IHCs and/or neurons are functioning less efficiently, or reduced in number, off-frequency listening may occur. Whilst such places upon the basilar membrane are not strictly 'dead', the larger stimulus necessary to produce basilar membrane vibration in that region will cause excitation of adjacent, healthier, more efficiently functioning IHCs / neurones. Clinical procedures used to

diagnose dead regions are based upon detection of off-frequency listening. It is also recognized however, that in instances where hearing impairments arise at adjacent regions of the basilar membrane, it may no longer be possible to determine a dead region through this process (Munro, 2007).

(ii) Timing & variability of occurrence

The variability of the timing of occurrence of dead regions was an interesting finding of the present study. To date, there has been no study looking at the presence of dead regions in patients who have had platinum based chemotherapy.

All 7 (9 ears) patients, who demonstrated dead regions, did show worsening of their hearing thresholds. Their hearing thresholds prior to chemotherapy ranged between 35 and 60 dB HL and at the time of dead region, the hearing thresholds were between 40 and 95 dB HL. Vinay & Moore (2007) described a high incidence of dead regions in adults with sensorineural hearing impairment, especially for frequencies at which the hearing loss exceeds 70 dB HL. In the present study, 6 out of 7 patients showed presence of dead regions at 3000 Hz and 4000 Hz. Aazh & Moore (2007) tested 98 people with absolute thresholds between 60 and 85 dB HL at 4 KHz using the threshold equalizing noise test for presence of dead regions, of which 36 had a dead region at 4 KHz. They found no statistically significant difference in the slope of the audiogram or PTA between ears with and without dead regions and the mean absolute threshold at 4 KHz was significantly higher for the group with dead region than for the group without dead region. The prevalence of dead region exceeded 50% for hearing losses greater than 70 dB.

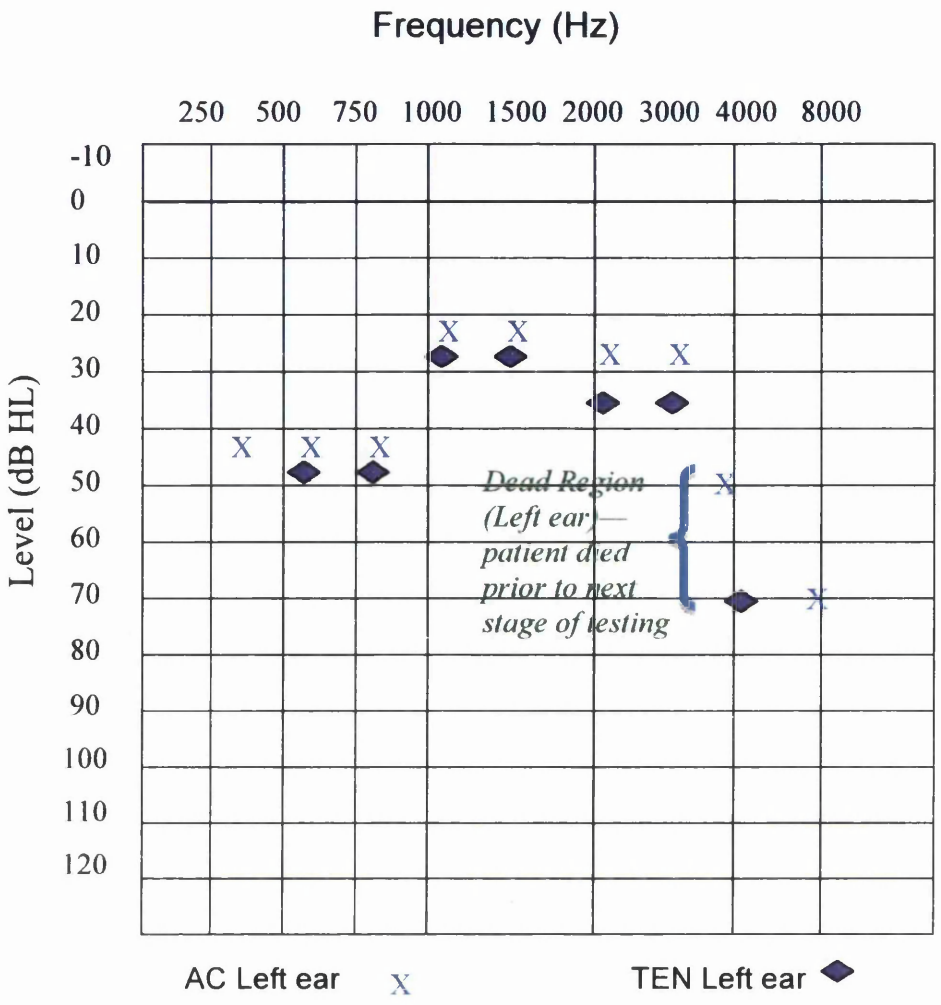
(iii) Presence at pre-chemotherapy stage

It has been reported in the literature about the association between a presence of dead regions, slope of the audiogram and degree of hearing loss. Vinay and Moore (2007) reviewed 308 patients with sensorineural loss for evidence of dead regions and found that for each test frequency, 59% or more of ears had a dead region when the absolute threshold was above 70 dB HL. A very steep slope of the audiogram is suggestive of a high-frequency dead region but does not provide a reliable diagnostic method. On the other hand, Aazh and Moore (2007) found no statistically significant difference in the slope of the audiogram between ears with and without dead regions. Jacob (2006) assessed 43 patients (76 ears) with high frequency sensorineural loss and identified

dead regions in 92% of seventy-six tested ears. This was in agreement with previous results that suggested a significant prevalence of dead regions in individuals with sloping sensorineural hearing loss (Moore, 2001 ; Vickers *et al.*, 2001). Summers (2003) used TEN and psychophysical tuning curves (PTC) to assess eighteen ears with moderate to severe sloping sensorineural hearing loss. Both tests were able to identify the presence or absence of dead regions in ten out of eighteen ears (56%). They concluded that a 56% agreement rate between two tests showed that at least one of them was partially reliable as a diagnostic tool. However, due to unrelated factors to the presence of dead regions, may lead to excess masking and not produce tip shifts in PTC and hence, PTC shifts are more reliable than TEN test when there is a disagreement between results of both tests. Davies (2009) investigated the prevalence of cochlear dead regions in 62 patients with sensorineural hearing loss. TEN test was used to assess the presence or absence of dead regions with prevalence of cochlear dead regions being 14.5% among patients. Absolute thresholds at 4 KHz tended to be higher in the patients with dead regions, but presence or absence of dead regions was not related to the slope of the audiogram or pure tone average of 500hz, 1kHz, 2kHz & 4kHz.

However, the present study highlighted an interesting finding of presence of dead regions in five patients at pre- chemotherapy stage of testing without any of them having any previous history of chemotherapy with platinum based drugs, loud noise exposure, radiotherapy or use of any ototoxic drugs. Their hearing thresholds, at time of dead region, ranged between 60 and 85 dB HL and frequencies involved were 4KHz and 8 KHz, except in one case where frequencies between 1 KHz to 2 KHz were affected.

One such case is highlighted below as an example.



Patient with dead region at Pre chemotherapy testing

(iv) Spontaneous resolution

Another notable finding was the spontaneous resolution of the dead regions in three patients with improvement of hearing threshold in all but one case. In principle, the IHCs and/or neurones could be completely non-functional as a result of drugs or metabolic disturbance, but recover when the drug is removed or there is a recovery from metabolic disturbance (Moore, 2009-personal communication). Smoorenburg (1999) conducted studies to assess if cisplatin induced ototoxicity can recover spontaneously and measured response with electrocochleography. They strongly suggested that spontaneous recovery of cochlear injury can occur in the mature mammalian cochlea and it may be possible to stimulate recovery from acute hearing loss using neuropeptides. Monitoring of hearing loss during chemotherapy, account of

total dosage received, co-administration of chemoprotective agents and allowing substantial clinically acceptable breaks between chemotherapy cycles may allow the cochlea to recover spontaneously from the ototoxic effects of chemotherapeutic agents.

(v) Oxaliplatin & dead regions

Dead regions were observed in three patients who received Oxaliplatin, with none of them having previous history of hearing loss, use of ototoxic drugs or loud noise exposure. There was worsening of their audiometric threshold, at the frequency of dead region, in comparison to the pre-chemotherapy stage by more than 20 dB HL in two patients. In one patient, the dead region spontaneously improved on further testing. On reviewing the literature (search term: Oxaliplatin AND / OR hearing loss: 1966 to date) , there has been only one report of a case of oxaliplatin induced hearing loss. Malhotra (2010) reported unilateral hearing loss in a 70-year-old woman who was undergoing postoperative chemotherapy for rectal adenocarcinoma and had developed hearing loss following a single infusion of Oxaliplatin, which persisted and never recovered. Hellberg (2009) conducted a study to determine why Oxaliplatin has negligible otoxicity when compared with cisplatin, despite both being platinum compounds. They measured the amount of cisplatin and oxaliplatin that reached the cochlea in guinea pigs following intravenous dosing of each drug and concluded that cisplatin, and not Oxaliplatin, induced apoptosis, which involved superoxide-related pathways. There was a lower cochlear uptake of oxaliplatin than cisplatin, thereby explaining oxaliplatin's lower ototoxic potential.

8.3 Limitations

During the present study, dead regions were identified in 7 patients (9 ears) at various stages of TEN testing. The variability of the occurrence of the dead regions was an important observation made during this study. Cairns (2007) reviewed short-term test-retest repeatability of the TEN (HL) test on 15 teenagers (mean age 14 years) with long-standing severe-to-profound hearing impairment, and 20 adults (mean age 74 years) with moderate- to-severe hearing impairment using the same equipment and procedure, after an interval of less than five days. They found that only 2 ears (8%) in teenagers and 3(7.5%) in adults changed category on retesting and overall the TEN

test repeatability was good. They concluded that the majority of ears that changed category on retest had just met the dead-region criteria at an isolated frequency and hence immediate retest is worthwhile in such cases. In the present study, all the cases met criteria of dead region for the TEN test (Moore, 2004) and it was not possible to recall them for TEN test repeatability, as the cohort of patients comprised people with cancer.

8.4 Future implications

Identification of dead regions in 7 patients (9 ears) was an important outcome of the present study, as it highlighted that platinum based drugs could cause dead regions. TEN (HL) test, therefore, could be valuable in monitoring hearing loss in patients receiving platinum based chemotherapy. Moore (2004) suggested that there is no value in amplifying frequencies that lie within the dead region. However, in people with high frequency hearing loss, as is the case with people having platinum based chemotherapy, applying amplification for frequencies up to 50% higher than the lower edge frequency of the dead region may be of benefit. This can help to avoid distortion and acoustic feedback, thereby allowing a better assessment and fitting of hearing aids. Accurate documentation of dead regions using the TEN (HL) test would help in selection of candidates for novel forms of hearing aids and their rehabilitation.

8.5 Further research

The present study highlighted some interesting observations. These were:
(i) Platinum based chemotherapy does lead to dead regions but at variable times.
(ii) Oxaliplatin can lead to dead regions
(iii) Dead regions can spontaneously resolve in patients on chemotherapy
The newer version of the TEN test is a fast and efficient way of detecting dead regions (Moore, 2004). However, further research is required to verify the suitability of TEN (HL) criteria for dead region detection in various age groups and degrees of SNHL (Cairns *et al.*, 2007). It is acknowledged the TEN test (HL) is relatively quick and useful in establishing the presence of dead regions, yet it only approximates the value of the frequency at the edge of dead region (f_e), provided appropriate measures are taken to prevent the detection of beats and simple difference tones,

Psychophysical Tuning Curve (PTC) are useful in estimating f_e more precisely, particularly where the TEN may produce borderline results (Moore *et al.*, 2000; Moore and Alcántara, 2001; Vestergaard, 2003; Kluk and Moore, 2006).
Kluk and Moore (2006) and Sek (2005) suggested that fast PTCs be more readily available to clinicians for clinical practice due to their being quick to perform and precise f_e estimate, although not always the case. TEN and PTCs (traditional or fast) should be used in combination, where dead regions are suspected, thus quickening the process of identifying dead regions and their boundaries.
Further research needs to be done to look at Oxaliplatin and dead regions, as well as the spontaneous resolution of the dead regions by combining both TEN (HL) test and fast PTCs.

8.6 Conclusion

In summary, the primary aim of this study was to identify dead regions in the cochlea in patients who had chemotherapy with platinum based drugs using the Threshold Equalising noise (TEN HL) test. Fifty patients were recruited for the study. The present study highlighted some interesting observations. These were:
(i) Platinum based chemotherapy administration led to dead regions in seven patients.
(ii) Dead regions were observed in three patients who received Oxaliplatin
(iii) Spontaneous resolution of the dead regions was observed in three patients, who received platinum based chemotherapy.
(iv) Dead regions occurred at different times during the study and did not have a specific pattern
The above findings were very interesting to note and notably will require further research.

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APPENDIX

1. Patient information sheet

1. Study title

Evaluation of TEN HL (threshold equalising noise) test to localise dead regions within the cochlea in patients who have had chemotherapy with platinum based drugs.

2. Invitation paragraph

You are being invited to take part in a research study. Before you make your decision, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and to discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 OBW.

Thank you for reading this

3. What is the purpose of the study?

Cisplatin and carboplatin are highly effective drugs, that are used in the treatment of your cancer. As you know there are several side effects of these drugs. One of which is the possibility of hearing loss. They affect the hearing by damaging hair cells in the cochlea (organ of hearing). Our study is to assess the amount of hearing loss, if any by using a simple hearing test called the TEN (Threshold Equalizing Noise) test.

4. Why have I been chosen?

Any patient who is on platinum based drugs such as yourself may be invited to take part in this study. We aim to recruit 50 patients over a period of 24 months for a long term study.

5. Do I have to take part?

Your participation in this study is entirely voluntary. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a consent form.

You are under no pressure to take part and may withdraw from the study if you so desire at any time without having to explain why. This will in no way affect the standard of care you receive.

6. What will happen to me if I take part?

You will be required to come for the hearing test, at a time convenient to you once before and once one month after completion of your treatment. There will be two more visits 6 months and 12 months following completion of your treatment (four tests in all). The hearing test will be done in the ENT outpatients department, Singleton Hospital by myself (Mr.S.Berry).
You will not need to visit your GP more often than for your usual treatment

7. What do I have to do?

Taking part in the study does not require you to do anything different from other patients who undergo the same treatment apart from having hearing tests.

8. What is the drug or procedure that is being tested?

The aim of the study is to find out the effects of platinum based drugs on hearing by using a simple hearing test as mentioned above.

9. What are the side effects of any treatment received when taking part?

None

10. What are the possible disadvantages and risks of taking part?

None

11. What are the possible benefits of taking part?

There is no intended clinical benefit to you from taking part in the study. But the information we get from the study may help other patients in the future.

12. What if new information becomes available?

If new information becomes available about the effects of anti-cancer drugs on cochlea, this will be conveyed to you in the following visit to the hospital. The planned follow up contacts with you will proceed as normal.

13. What happens when the research study stops?

When the research ends, we will tell you about our findings and discuss with you at that time any further treatment you may require.

14. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

15. Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be identified.

16. What will happen to the results of the research study?

We hope to complete the study in 24 months time. We will then produce a report and papers will be written for publication in medical journals. Your identity will remain confidential in all these reports.
In addition we will write to tell you the main results of our research.

17. Contact for Further Information

Mr Sandeep Berry, SpR ENT	07977118685
Mr Simon Browning, Consultant ENT Surgeon	01792205666 ext: 5567

8. Patient consent sheet
Centre Number: :
Study Number:
Patient Identification Number for this trial:

2. Patient consent sheet

CONSENT FORM

Title of Project:

Evaluation of TEN (threshold equalising noise) test to localise dead regions within the cochlea in patients who have had chemotherapy with platinum based drugs.

Name of Researcher: Mr. S. Berry

Please initial box

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

Name of Patient

Date

Signature

Name of Person taking consent
(if different from researcher)

Date

Signature

Researcher

Date

Signature